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JOURNAL DE LA SOCIÉTÉ CANADIENNE DES ANESTHÉSISTES

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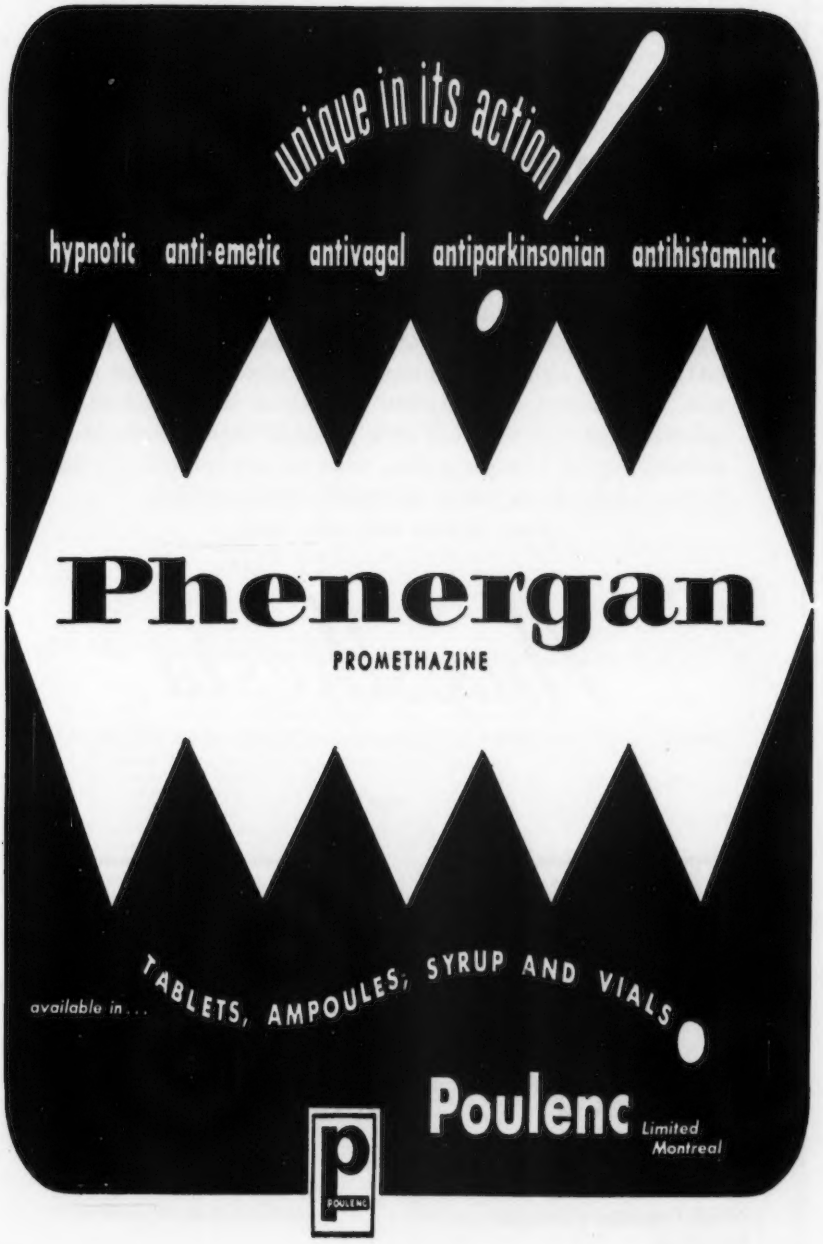
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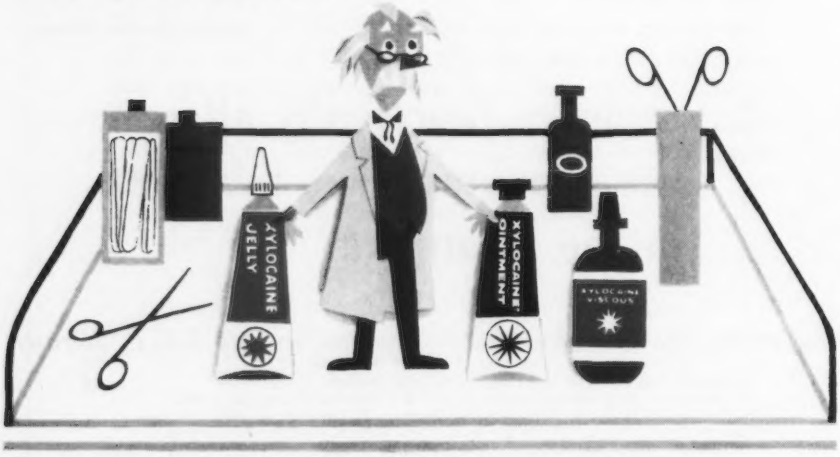

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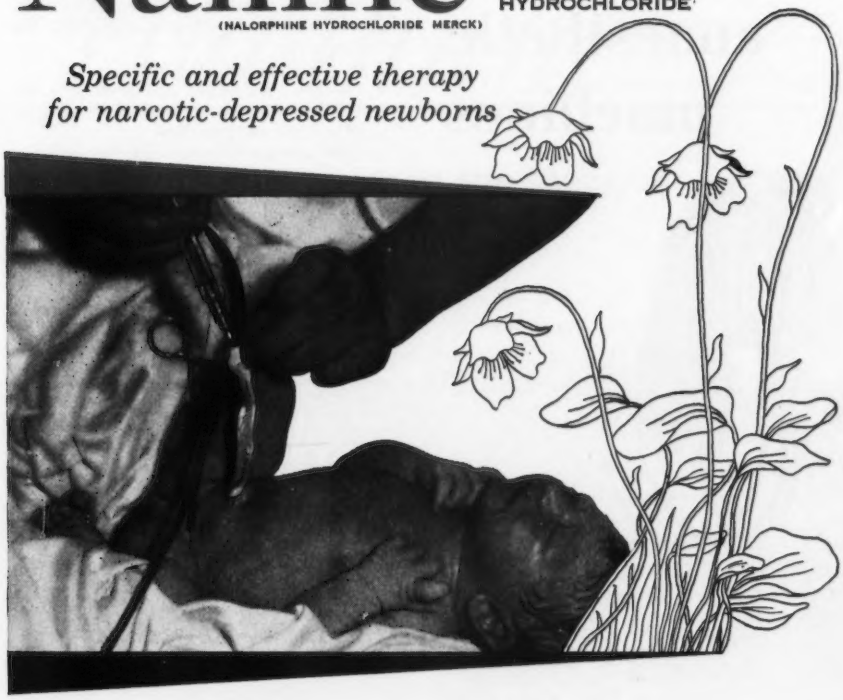

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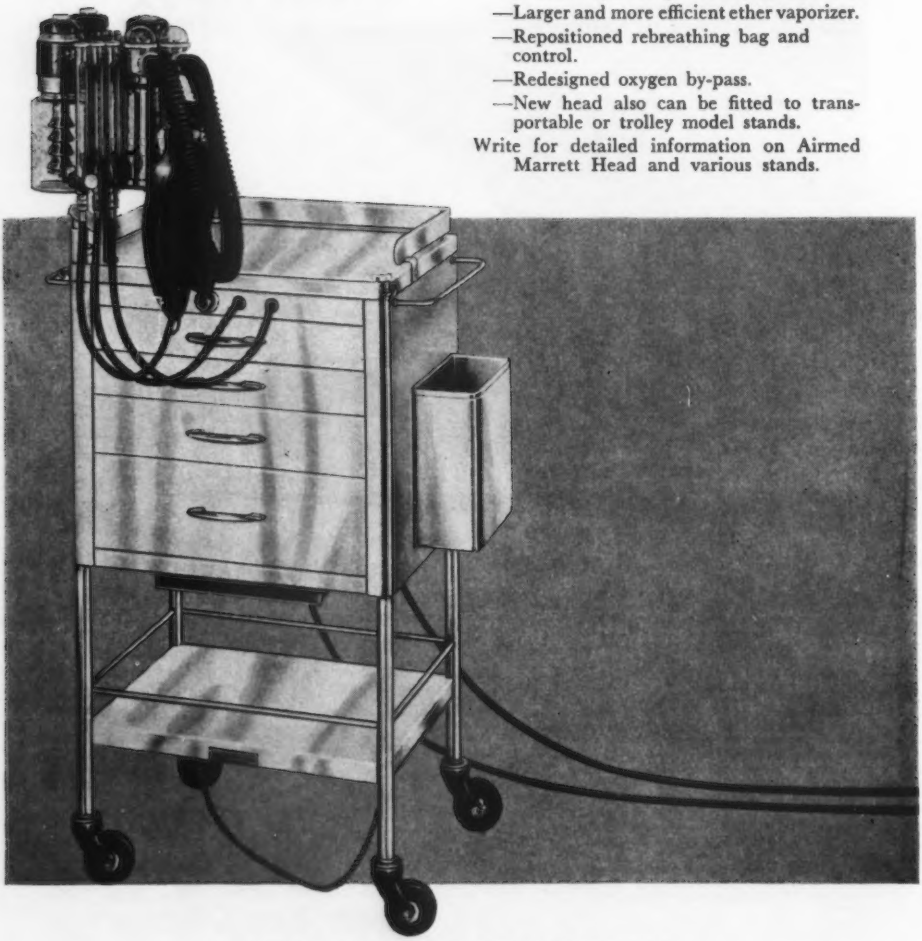

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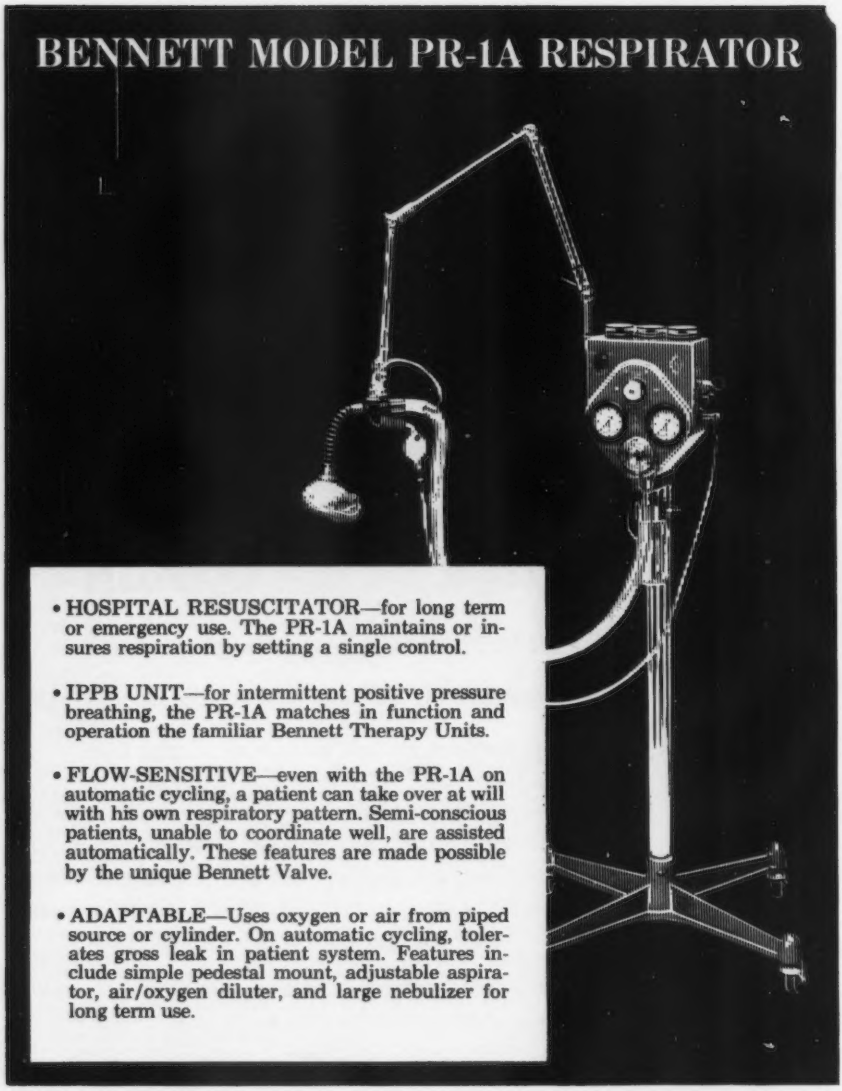

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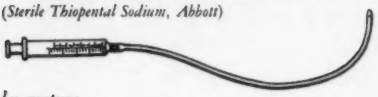

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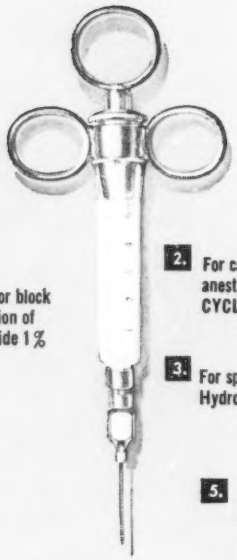

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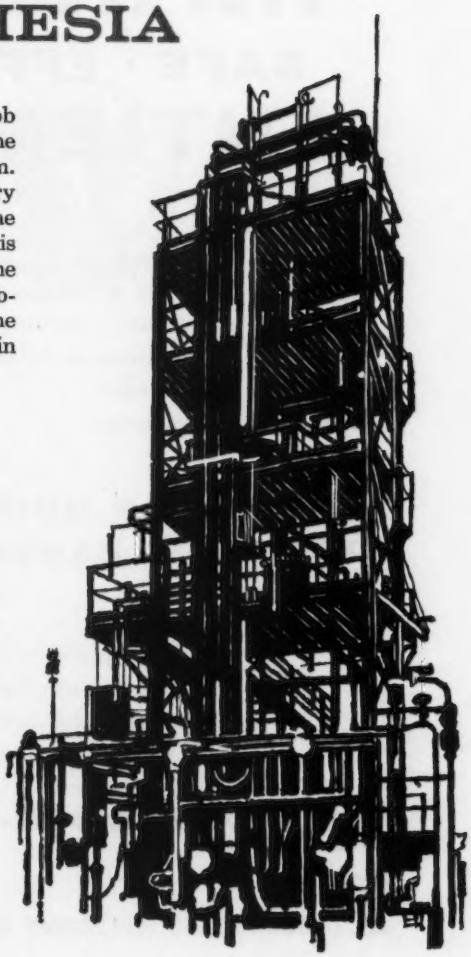

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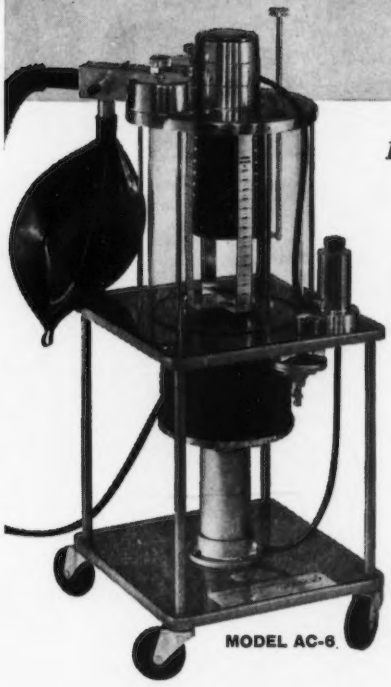

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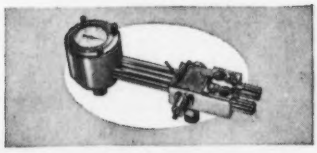

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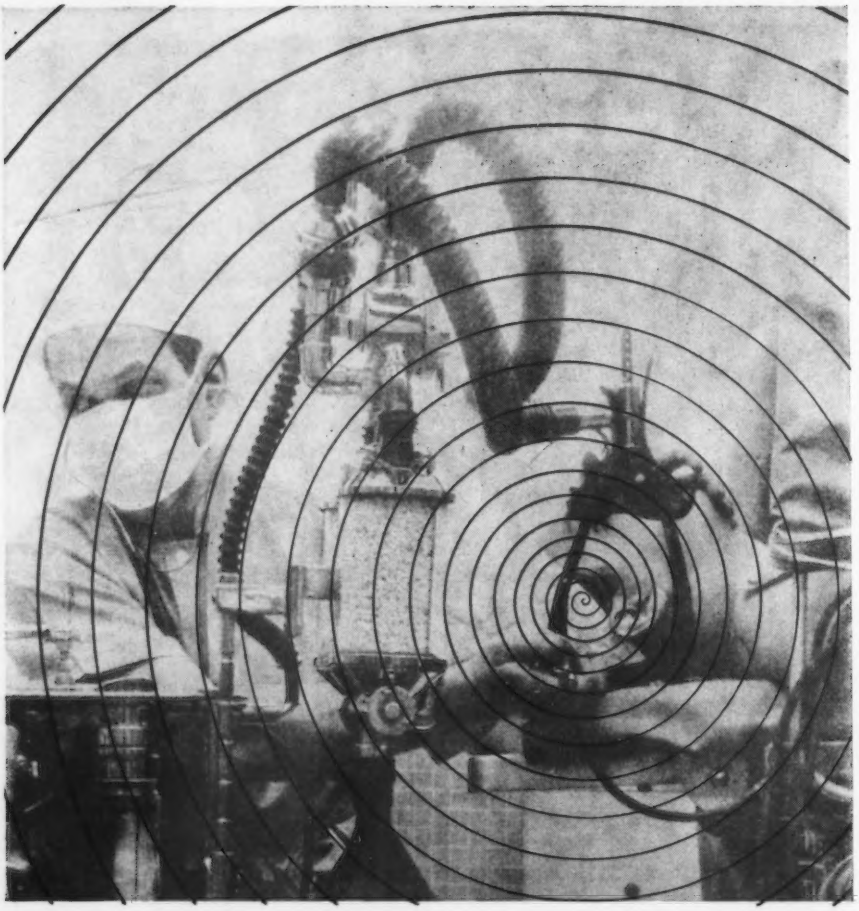

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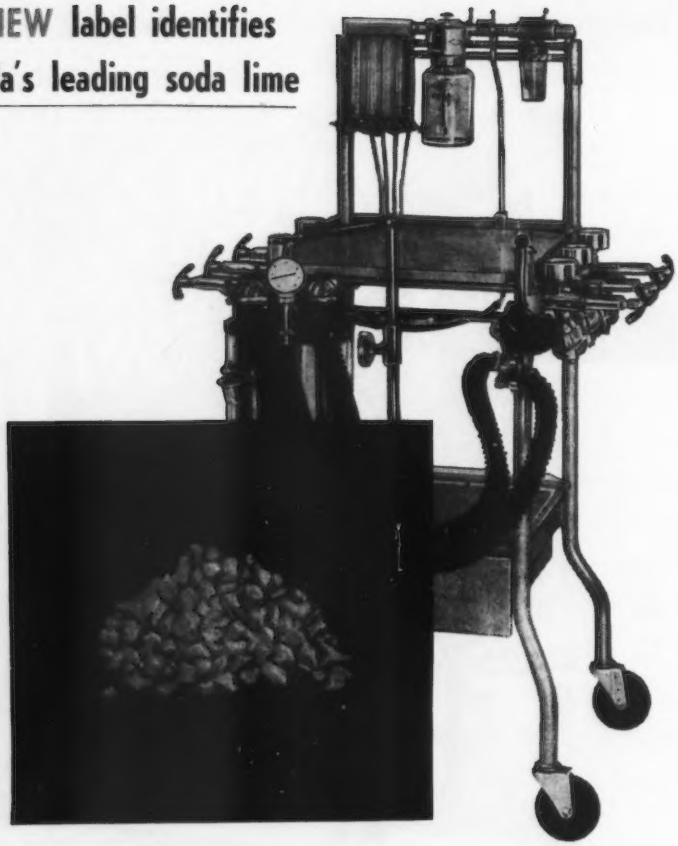

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EDITORIAL

"Blood, Sweat, and Tears"

The medical profession in co-operation with public health officials has successfully reduced the maternal mortality rate during the past three hundred years. In London, England, the rate in 1660 was 250 per 10,000. This rate had dropped to 40 per 10,000 by 1881, and 30 per 10,000 by 1941. In 1956 the maternal death rate in Canada was 8 per 10,000, and in the U.S.A., 12 per 10,000.

Haemorrhage during child-birth still remains a major factor contributing to maternal mortality. Fibrinogen deficiency leading to uncontrollable haemorrhage has been of great interest and concern to many of us, and is a major cause of maternal deaths.

The haemorrhagic condition resulting from a deficiency of fibrinogen is a most serious complication of pregnancy. It is most essential that the attending obstetrician and anaesthetist be on the alert for this condition, investigate quickly, institute proper treatment instantly, and avoid other procedures that may complicate the recovery of the patient. Afibrinogenaemia is not a new condition in medical science. However, its increasing frequency in the past few years has made it imperative that we, as anaesthetists, review its diagnosis, treatment, and complications. We should also review the mechanism of blood-clotting, and examine closely the role of fibrinogen in this complicated physiological action. We should be aware that in certain obstetrical conditions tissue thromboplastin may enter the blood stream and reduce the amount of fibrinogen circulating in the maternal blood to a dangerously low level, leading to severe and often fatal haemorrhage.

Afibrinogenaemia is most commonly associated with abruptio placentae, retained dead foetus, amniotic fluid embolism, eclampsia, abortion, and retained placenta. (Metastatic carcinoma of lung, prostate, and pancreas may produce an analogous condition.)

If afibrinogenaemia is suspected, a quick practical test of fibrinogen levels is available and should be performed immediately. The Fibrindex test, which utilizes thrombin to test the coagulating ability of the blood, is quick and easy to perform. At the same time that the blood is drawn, an oxalated specimen should be set aside for a quantitative estimation of fibrinogen. This Fibrindex test should be repeated every two hours until the situation is under control.

The normal plasma level of fibrinogen in adults is 200–400 mg. per 100 ml. Pregnant women at term have somewhat higher levels of 300–500 mg. per 100 ml. It has been established that (*a*) when the plasma fibrinogen level falls below 150 mg. per 100 ml., oozing of blood may occur from any raw surface (e.g., the placental site); and (*b*) when the level falls below 100 mg. per 100 ml., severe haemorrhage will ensue that is impossible to control by local treatment at the bleeding site.

If these tests indicate that afibrinogenaemia has occurred, fibrinogen should be administered. The usual dose is 4 gm., but up to 12 gm. have been used. If

fibrinogen is not available, dried plasma should be used. Blood in large quantities, 2,000 to 4,000 cc., must be used. The blood substitutes, such as dextran and P.V.P., should be used with caution, as they may combine with up to 10 per cent of the circulating fibrinogen. Cortisone has been used with some success. It is also agreed that the coagulation defect should be corrected before further obstetrical procedures are performed.

Every refrigerator in every case room in every hospital, large or small, in Canada should contain the FIBRINDEX PREPARATION *for testing fibrinogen deficiency, and* DRIED FIBRINOGEN *for its treatment.*

The heading of this editorial is "Blood, Sweat, and Tears." Picture a case-room floor covered with blood, a perspiring anaesthetist, a pale obstetrician, and a dead or dying mother. Think of the tears to be shed by the bereaved husband and motherless children.

We, as anaesthetists, may be able to help prevent such a tragedy.

H. B. GRAVES, M.D.

"DU SANG, DES SUEURS ET DES PLEURS"

LA PROFESSION MÉDICALE, en collaboration avec les officiels de l'hygiène publique, ont réussi à réduire le taux de mortalité maternelle durant les trois cents dernières années. A Londres, en Angleterre, le taux était, en 1660, de 250 par 10,000. Ce taux est tombé, en 1881, à 40 par 10,000 et, en 1941, à 30 par 10,000. En 1956, au Canada, le taux de la mortalité maternelle était de 8 par 10,000 et aux Etats-Unis de 12 par 10,000.

L'hémorragie durant l'accouchement demeure encore un facteur important conduisant à la mortalité maternelle. La déficience de fibrinogène entraîne des hémorragies incontrôlables; cela a attiré l'attention et fait le souci d'un certain nombre de confrères car c'est une cause importante dans le nombre de morts maternelles.

L'hémorragie favorisée par une déficience en fibrinogène est, au cours de la grossesse, une complication des plus sérieuses. Il est de première importance que l'obstétricien et l'anesthésiste en service soupçonnent la possibilité de cette pathologie, fassent rapidement les recherches nécessaires, donnent instantanément le traitement adéquat et évitent les autres manœuvres qui pourraient compliquer la convalescence de la malade.

L'afibrinogénémie n'est pas une nouvelle entité en médecine. Mais son apparition de plus en plus fréquente au cours des dernières années nous oblige, nous anesthésistes, à revoir l'étude de cette pathologie et à nous tenir prêts à faire son diagnostic, son traitement et à éviter ses complications.

Il s'imposerait de repasser le mécanisme de la coagulation du sang et d'examiner attentivement le rôle du fibrinogène et de son action physiologique compliquée. Il faudrait savoir que, dans certains cas d'obstétrique, la thromboplastine tissulaire peut entrer dans le courant sanguin et produire, dans le sang maternel, un taux de fibrinogène dangereusement bas, pouvant conduire à des hémorragies graves et souvent mortelles.

L'afibrinogénémie est le plus souvent accompagné de décollement prématuré du placenta, de retention de fœtus mort, d'embolie de liquide amniotique, d'éclampsie, d'avortement, de retention placentaire (on peut découvrir une pathologie semblable dans les cas de métastases de carcinome du poumon, de la prostate et du pancréas).

Si l'on soupçonne l'existence de cette pathologie, il existe un test pratique et rapide des taux de fibrinogène, il faudrait les exiger immédiatement. Le test "Fibrindex" au cours duquel l'on se sert de thrombine pour évaluer la capacité de coagulation des sangs douteux est court et facile à faire. Au moment du prélèvement, on garde un échantillon de sang oxalté pour faire une mesure quantitative du fibrinogène. Il faut répéter ce test "Fibrindex" à toutes les deux heures jusqu'à ce que la situation soit normale.

Chez les adultes, le taux normal de fibrinogène dans le plasma est de 200 à 400 mg. pour cent. Les femmes enceintes à terme conservent un taux légèrement plus élevé soit de 300–500 mg. pour cent. On a démontré que (*a*) lorsque le taux de fibrinogène dans le plasma s'abaisse au-dessous de 150 mg. pour cent, il peut se produire un suintement sanguin de toute surface cruentée (e.g., site d'implantation placentaire), et (*b*) lorsque le taux tombe à 100 mg. pour cent, il va s'ensuivre une hémorragie grave qu'il devient impossible de contrôler en faisant un traitement local où siège l'hémorragie.

Si les tests révèlent la présence d'afibrinogénémie, il faut donner du fibrinogène. La dose ordinaire est de 4 g. mais l'on a déjà donné 12 g. Si l'on n'a pas de fibrinogène, il faut employer du plasma desséché. Il faut donner du sang en grandes quantités, de 2,000 à 4,000 cc. Il faut se servir avec prudence des substituts du plasma, comme dextran et P.V.P., car ces produits s'accaparent de 10 pour cent du fibrinogène circulant. On a employé la cortisone avec un succès relatif. L'on conviendra également qu'il faut corriger le défaut de coagulation avant d'entreprendre toute autre manœuvre obstétricale.

Dans tous les hôpitaux du Canada, petits ou grands, le réfrigérateur du laboratoire devrait contenir la préparation "Fibrindex" pour dépister la déficience en fibrinogène et du fibrinogène desséché pour la traiter.

Le titre de cet éditorial se lit "Du sang, des sueurs et des pleurs." Figurez-vous une salle où le plancher est couvert de sang, un anesthésiste en sueurs, un obstétricien tout pâle puis une mère à l'agonie ou déjà morte. Songez aux pleurs de l'époux et des orphelins.

En qualité d'anesthésistes, nous devrions pouvoir participer à la prévention d'une semblable tragédie.

H. B. GRAVES, M.D.

GUEST EDITORIAL

What the Obstetrician Expects and Hopes for from the Anaesthetist . . .

Discussions on this topic between obstetricians and anaesthetists generate more heat, more acrimony, and more hysteria than a husband and wife playing bridge together. Too often the situation involves two tired men, in the early hours of the morning, one at each end of the table. One resentful because he has made six telephone calls to get the man he may not want, who may have arrived just later than the psychological moment, so spoiling the obstetrician's extravagant promise to his patient of complete pain relief. The other resentful, knowing that he is probably the sixth call, that he may have been called too early, to help someone who may not be too competent; he may have to suffer capricious demands for a particular anaesthetic or commands that his unpremedicated patient, possibly with a full stomach, be alternately put down and let up for no apparent reason; he may have a difficult foetal resuscitation and all this for a patient who, as likely as not on receiving her account, will reply "I don't know you, I didn't ask for you, so I won't pay you!"

I say all this in a mood of sympathy—and it is in this mood that I will examine the problem.

It is a serious thought that maternal deaths from anaesthesia now comprise 3 to 5 per cent of all obstetric deaths, and appear to be increasing. It may be thought that this statement applies only to those areas in which a large percentage of anaesthesia is in the hands of the nurse anaesthetist, but this is not so. Dalziel (1) in a recent paper on "An Evaluation of Maternal Death Studies" states that between 1950 and 1955 out of a hundred maternal deaths in the Toronto area, eight were due to anaesthesia.

Difficult anaesthesia in the surgical field has made great strides in safety because it is only placed in the hands of highly trained anaesthetists: one has only to mention hypothermia, the extracorporeal circulation, the increasing use of relaxant. Yet obstetrics, the Cinderella of anaesthesia, in many centres still gets the leftovers, the untrained anaesthetist, the intern, nurse, medical student, or (probably safer) no one.

Analysis of obstetrical anaesthetic deaths reveals that it is not the agent that kills but the incompetent use of the agent. Incompetence here is not meant in any unkind way—it merely implies lack of training. In any survey attempting to decide what is the best anaesthetic for the obstetrical patient, the conclusion emerges that it is not the anaesthetic that matters, but the anaesthetist.

From this it follows that obstetricians would like—and the two patients involved deserve—not so much first-class anaesthesia as first-class anaesthetists. To put it another way: it is the man behind the mask that matters, not the mixture under the mask.

It is my belief that the safest, the most effective, and in the long run the most beneficial way to all concerned to provide obstetrical anaesthesia is with a 24-hour

coverage by the trained anaesthetist. This must always imply a reserve pool of other anaesthetists on call or supervised residents in training.

The anaesthetic service must have a large enough staff to ensure that no anaesthetist works more than every fourth or fifth night and that this tour of duty is rarely followed by an eight to two operating schedule next morning.

Do we, as obstetricians, have the right to demand this? When the situation is analysed, there is no doubt that both sides are happier under these conditions. Equally obvious, though, is the fact that it will only work satisfactorily under certain conditions.

First, either the hospital concerned must be virtually closed or the partnership concerned must operate virtually as a monopoly. Both these situations might invite valid criticism.

The next condition that must be overcome is the obstetrician's demand for a special anaesthetist rather than the man on duty. This may prove difficult.

Another disadvantage often cited is aptly illustrated in a paper by Hanley (2) entitled "Regional Anaesthesia in Obstetrics." The author—an obstetrician—contracted for obstetrical anaesthesia in a private closed hospital to be covered by a private anaesthesia clinic. This group anaesthetized 96 per cent of 20,000 deliveries, 99 per cent of which were carried out by the spinal or caudal technique.

As always, when this sort of paper is given at an obstetrical meeting, fierce discussion followed, ending in the conclusion that because in present-day obstetrics a high proportion of deliveries could be managed under minimal anaesthesia, this approach was like swatting a fly with a sledge hammer. It also bespoke considerable anaesthetic agility—or possibly over-anaesthetization.

I do not think an obstetrician has the right to demand or expect 24-hour coverage unless the group concerned is virtually closed. This is not always applicable, and until it is we will train our residents, and junior interns, in what appears to be statistically the safest method of anaesthesia—that is, pudendal block and self-administered trichlorethylene. We must rely on the trained anaesthetist for complicated procedures. This is safer than asking the untrained to undertake anaesthesia.

Do we have the right to expect the anaesthetist to be responsible for maternal and foetal resuscitation?

Unlike Vishnu, the obstetrician has only one pair of hands, and these should be enclosed in sterile gloves and fully occupied with the patient. The most dangerous time during delivery for both mother and baby is just before and just after the delivery of the placenta. At this stage it is dangerous for the obstetrician to leave his patient. It may also be dangerous for the anaesthetist. However, it is always a comfort—and I would say a necessity—to have an anaesthetist, competent to undertake foetal resuscitation, to take care of the first dangerous few minutes of a newborn baby's life.

In the matter of maternal resuscitation the interests of anaesthetist and obstetrician occasionally clash. The anaesthetist may not be keen to transfuse the patient under anaesthesia. On the other hand, an obstetrician feels that as long as he is in the driver's seat as far as blood replacement is concerned, he will not lose his patient from post-partum haemorrhage.

It must be remembered that a healthy pregnant woman can compensate very well for blood loss. She can withstand a loss of 1,000 cc. of blood without change in vital signs. A lowering of blood pressure, increase in pulse, coldness, and sweating all imply a blood loss of at least 1,500 cc. Therefore, I make a plea not to wait for change of blood pressure and pulse before transfusing the patient but rather to rely on the conscientious estimate of the amount of blood lost into the obstetrician's lap. This will allow resuscitation to be carried out while veins are plentiful rather than waiting until the inevitable collapse occurs following removal of the oxygen mask.

Lastly, it is my belief that a useful addition to the delivery suite would be a recovery room to take care of the post-partum patient during the so-called fourth stage of labour. So often collapse will sneak up on the patient because the nurse is unwilling to commit the social blunder of disturbing the husband holding hands with his wife.

Who will control the recovery room?—the 24-hour anaesthetist, of course.

So I do feel that the obstetrician is entitled to expect the anaesthetist to carry out maternal and foetal resuscitation.

Has the obstetrician the right to dictate the type of anaesthesia? My main theme is that we need trained anaesthetists. If properly trained the anaesthetist will know what is best for the patient and baby under the particular set of circumstances.

There are, of course, certain specialized situations in which the obstetrician should have a very definite say. But this usually devolves on the need of relaxation of the uterus for bringing down a leg in a breech presentation, or the desire for regional anaesthesia for prematurity, Caesarean section, or difficult mid-forceps delivery after a prolonged labour. It should be realized that although ether and breech extraction are traditionally associated, this type of anaesthesia is not necessary unless the legs are extended, making difficult intra-uterine manipulation mandatory.

There is now an increasing desire on the part of the patient for the awake delivery. This may be just a fashion of the time, but I think it should be fostered, if only to reduce foetal narcosis. The acme of satisfaction to the patient who desires this is a successful epidural anaesthesia. It does not need a brilliant prophet to say that skill in this type of anaesthesia will properly be the hallmark of the successful obstetrical anaesthetist. When anaesthetics are discussed with patients, they inevitably say once an epidural, always an epidural. Again, the disadvantage of over-anaesthetization must be guarded against.

Complementary to this, should the anaesthetist prescribe analgesia during the first stage of labour? After all, with 24-hour coverage he is there. I do not consider that analgesia during the first stage is premedication for operative delivery. The woman in the first stage of labour often needs the presence and moral support of her obstetrician rather than analgesia.

There is a trend towards lessened analgesia during labour. This is healthy and should be encouraged so long as it is not at the expense of desired pain relief. There is no doubt that rational psycho-prophylaxis has contributed to this trend

and it may be that one of the most important roles of the obstetrician is support in the first stage of labour.

Lastly, every analgesic and anaesthetic drug passes the placental barrier. The umbilical cord presents opportunity for easy simultaneous sampling of foetal venous and arterial blood. Therefore, in an area where very intensive research is going on into the materno-placental-foetal relation we would welcome our colleagues in the department of anaesthesia to add their co-operation.

As you can see, we are no happier than you are about the *dash in–clap on the mask–dash out* type of anaesthesia. We would like to see the difficult art of obstetrical anaesthesia receiving the same consideration as surgical anaesthesia.

What the obstetrician expects and hopes for, then, is a completely trained anaesthetist who will relieve him of the anxiety of thinking of the top end of the patient or of her baby, once it is delivered; who will carry out prompt maternal and foetal resuscitation; and who may look after the patient in a recovery room. In short, we are asking for a friend in need. In the vast majority of cases we get him.

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ÉDITORIAL INVITÉ

A QUOI L'OBSTÉTRICIEN S'ATTEND-IL ET QU'EST-CE QU'IL ESPÈRE DE L'ANESTHÉSISTE?

LES DISCUSSIONS sur ce sujet entre obstétriciens et anesthésistes engendrent plus de chaleur, d'acrimonie et d'hystérie que lorsqu'un époux joue au bridge avec son épouse.

Trop souvent la situation met en présence deux hommes fatigués, aux petites heures du matin, un à chaque bout d'une table. D'une part, un homme en furie qui a dû faire six appels téléphoniques pour atteindre celui qu'il préférait ne pas avoir et celui-ci est arrivé juste après le moment psychologique, faisant manquer la promesse extravagante de l'obstétricien à sa malade qu'elle accoucherait sans douleur. D'autre part, un homme, en furie également, sachant qu'il a été appelé probablement le sixième, peut-être trop tôt, pour aider quelqu'un qui n'est peut-être pas trop compétent; il peut avoir à subir des demandes capricieuses pour un anesthésique particulier ou à faire face à des exigences que cette malade sans prémédication qui a probablement l'estomac plein, soit alternativement endormie et réveillée sans raison; il est également possible qu'il ait à faire une ressuscitation fœtale difficile et, tout cela, pour une malade qui lui dira en recevant son compte: "Je ne vous connais pas, je ne vous ai pas demandé, en conséquence je refuse de vous payer."

Je raconte cela avec un esprit de compassion et c'est dans cet état d'esprit que je veux étudier le problème.

C'est un fait tragique que, actuellement, 3 à 5 pour cent de toutes les morts obstétricales soient dues seulement à l'anesthésie et que ce pourcentage semble aller en augmentant. On pourrait croire que cette affirmation ne s'applique que pour les régions où un fort pourcentage des anesthésies sont administrées par des garde-malades, mais ce n'est pas le cas. Dalziel (1), dans un article intitulé "An Evaluation of Maternal Death Studies," affirme que, entre 1950 et 1955, dans les environs de Toronto, sur cent morts maternelles, huit étaient dues à l'anesthésie.

En chirurgie, l'anesthésie difficile a beaucoup gagné en sécurité parce qu'elle est placée seulement dans les mains d'anesthésistes bien qualifiés: l'on a seulement qu'à mentionner l'hypothermie, la circulation extra-corporelle, l'emploi de plus en plus fréquent de myorésolutifs. Par contre, en obstétrique, le Cinderella de l'anesthésie, dans plusieurs centres, demeure le mis-de-côté, l'anesthésiste inexpérimenté, l'interne, la garde-malade ou l'étudiant en médecine ou encore (peut-être pour plus de sécurité) personne.

L'analyse des morts en obstétrique nous permet d'affirmer que ce n'est pas l'agent qui tue mais l'usage incompétent de cet agent. Ici, le mot incompétence ne signifie pas maladroit, mais simplement qui manque d'entraînement et d'expérience. Tous les auteurs qui ont voulu désigner le meilleur agent anesthésique pour la malade en couches en sont venus à la conclusion que ce n'est pas l'agent anesthésique qui compte mais plutôt l'anesthésiste.

Il découle de cela que les obstétriciens préféreraient, et les deux malades en cause le méritent, plutôt qu'un agent anesthésique de première classe, des anesthésistes de première classe. En d'autres termes, ce n'est pas le mélange sous le masque qui compte, mais l'homme qui tient le masque.

A mon avis, la façon la plus sure, la plus efficace et, à tous points de vue, la plus profitable, est d'avoir, en obstétrique, un anesthésiste expérimenté 24 heures par jour. A part cela, il devrait y avoir d'autres anesthésistes disponibles sur appel ou des résidents à l'entraînement sous surveillance.

Le service d'anesthésie doit être assez considérable pour que l'anesthésiste soit assuré de ne pas faire de travail nocturne plus souvent qu'à toutes les quatre ou cinq nuits et que cette garde ne soit que rarement suivie pour lui d'un programme opératoire de huit heures à deux heures le lendemain.

En qualité d'obstétriciens, avons-nous le droit d'exiger cela? Après analyse de la situation, il ne fait aucun doute que les deux partis en présence sont plus heureux dans ces conditions. Toutefois, ce n'est qu'après certaines conventions que le système fonctionnera de façon satisfaisante.

D'abord, ou bien l'hôpital en cause doit fonctionner comme un hôpital fermé ou l'association doit travailler comme un monopole. Ces deux situations sont en proie à des critiques justifiées.

Une autre difficulté à surmonter c'est le fait qu'un obstétricien demande un anesthésiste spécial de préférence à celui qui est de garde. Cela peut créer des difficultés.

Il existe un autre ennui qu'on mentionne souvent auquel Hanley (2) fait allusion dans un article intitulé "Regional Anaesthesia in Obstetrics." L'auteur—un obstétricien—prenait entente pour l'anesthésie en obstétrique dans un hôpital privé fermé et cet hôpital était desservi en anesthésie par une clinique privée de spécialistes. Ce groupe d'anesthésistes a donné l'anesthésie à 96 pour cent de 20,000 accouchées et 99 pour cent d'entre elles ont reçu des rachianesthésies ou des caudales.

Comme toujours, lorsqu'une statistique comme cella-là est présentée à une assemblée d'obstétriciens, il s'ensuit une vive discussion dont il faut conclure que, parce que, de nos jours, une grande proportion des accouchements peut se faire avec un minimum d'anesthésie, ce procédé ressemble à la poursuite d'une mouche avec un marteau. Cela suppose également une grande agilité anesthésique ou encore il n'est pas impossible que cela entraîne une anesthésie excessive.

Je ne crois pas qu'un obstétricien ait le droit de demander ou de s'attendre à un service de 24 heures si le groupe en cause n'a pas l'exclusivité. Cela n'est pas toujours possible et d'ici à ce que cela le soit, nous allons enseigner à nos résidents, à nos internes juniors ce qui semble, d'après les statistiques, la méthode la plus sure en anesthésie: le blocage honteux et le trichlorethylène administré par la malade elle-même. Il nous faut compter sur un anesthésiste expérimenté pour les cas compliqués. Ce système offre plus de sécurité que de demander à une personne inexpérimentée de pratiquer l'anesthésie.

Avons-nous le droit de nous attendre que l'anesthésiste se tienne responsable de la ressuscitation de la mère et de l'enfant?

A la différence de Vishnu, l'obstétricien n'a qu'une paire de mains qui doivent être couvertes de gants stériles et toutes vouées à la malade. Le moment le plus dangereux, au cours d'un accouchement, aussi bien pour la mère que pour l'enfant, c'est immédiatement avant et immédiatement après la sortie du placenta. A ce moment-là, il serait dangereux que l'obstétricien laissât sa malade. Le danger existe également pour l'anesthésiste. Toutefois, c'est toujours réconfortant —et je dirais même une nécessité—que d'avoir un anesthésiste compétent pour entreprendre la ressuscitation fœtale, pour prendre soin des premières dangereuses minutes de la vie de l'enfant qui vient de naître.

Quand il s'agit de la ressuscitation maternelle, il peut arriver que les intérêts de l'anesthésiste et de l'obstétricien s'entrechoquent. L'anesthésiste peut ne pas être disposé à transfuser une malade sous anesthésie. Par contre, l'obstétricien a le sentiment qu'aussi longtemps qu'il a la commande en ce qui concerne la transfusion, il ne perdra pas sa malade d'hémorragie post-partum.

Il ne faut pas oublier qu'une femme enceinte en santé peut compenser ses pertes de sang avec facilité. Elle peut supporter une perte de 1,000 cc. de sang sans modification de ses signes vitaux. Une chute de tension artérielle, un rythme cardiaque accéléré, de la froideur des extrémités, de la transpiration supposent une perte de 1,500 ml. de sang au moins. C'est pourquoi je conseille de ne pas attendre, pour transfuser une malade, des changements de pouls et de tension mais de se fier à une évaluation consciencieuse de la quantité de sang perdu devant l'obstétricien. Cela permettra de faire la ressuscitation au moment où les veines sont encore remplies plutôt que d'attendre que le collapse inévitable survienne après on a enlevé le masque à oxygène.

Enfin, j'ai la conviction que ce serait une précieuse acquisition que d'avoir une salle de réveil attenante à la salle d'accouchement pour surveiller la parturiente dans ce qu'on appelle la quatrième période du travail. Bien souvent le collapse va s'amorcer chez une malade parce que la garde-malade ne veut pas commettre la bévue sociale de déranger l'époux qui tient la main de son épouse.

Qui devra faire la surveillance de la salle de réveil? L'anesthésiste et durant 24 heures.

En définitive, je crois que l'obstétricien a le droit de s'attendre à ce que l'anesthésiste assume la responsabilité de la ressuscitation maternelle et fœtale.

L'obstétricien a-t-il le droit d'imposer le genre d'anesthésie? Ma politique est que nous avons besoin d'anesthésistes expérimentés. S'il possède une expérience adéquate, l'anesthésiste saura faire le choix le plus propice à la mère et à l'enfant dans les circonstances particulières où il se trouvera.

Toutefois, il se rencontre des situations bien particulières où l'obstétricien devrait s'imposer. Mais cela concerne habituellement le besoin d'atonie utérine pour descendre une jambe dans une présentation de siège ou une demande de régionale au début du travail; ou encore pour une césarienne ou un forceps moyen difficile après un travail prolongé. Il faut tout de même se rendre compte que, même si l'éther et une extraction par le siège sont presque toujours associés, cette sorte d'anesthésie n'est pas nécessaire à moins que les jambes soient étendues, nécessitant une manipulation intra-utérine difficile.

Actuellement, de la part de la malade, on exprime le désir d'accoucher sans perdre conscience. Il est possible qu'il ne s'agisse que d'une mode passagère mais je crois qu'il faille encourager la chose ne serait-ce que pour réduire la narcose fœtale. Pour une malade qui manifeste ce désir, il n'y a rien de mieux qu'une épidurale réussie. Il n'est pas nécessaire d'être un brillant prophète pour affirmer que, dans ce genre d'anesthésie, la dextérité va être le barême du succès pour l'anesthésiste en obstétrique. Si l'on en parle aux malades, cela devient inévitablement une fois une épidurale, toujours une épidurale. Encore une fois, il faut éviter l'excès d'anesthésie.

Pour compléter le tableau, l'anesthésiste devrait-il prescrire l'analgésie au cours du premier stage du travail? Après tout, il est là puisqu'il donne un service de 24 heures. Je ne suis pas d'avis que l'analgésie durant le premier stage est l'équivalent de la prémédication pour le moment de l'accouchement. Au cours de cette première période du travail, la malade a souvent plus besoin de la présence et du support moral de son accoucheur que d'analgésie.

On observe une tendance à diminuer l'analgésie durant le travail. La chose est bonne, il faut l'encourager aussi longtemps que cela ne va pas l'encontre du désir d'être soulagée. Il ne fait pas de doute que la prophylaxie psychique rationnelle n'est pas étrangère à cette tendance et ce support, durant la première période du travail, devient une des fonctions les plus importantes de l'obstétricien.

Enfin, tous les analgésiques et les anesthésiques traversent la barrière placentaire. Le cordon ombilical offre une opportunité unique de prélever facilement et simultanément du sang veineux et du sang artériel. En conséquence, dans les endroits où l'on poursuit des recherches intensives sur la relation mère-placenta-fœtus, nous souhaiterions la plus cordiale bienvenue à nos collègues du service d'anesthésie pour exercer leur coopération.

Comme vous pouvez le constater, nous ne sommes pas plus emballés que vous ne l'êtes du genre d'anesthésie: entre à la course, saisis le masque et sors aussi vite. Nous aimerions que l'art difficile de l'anesthésie obstétricale reçoive la même attention que l'anesthésie chirurgicale.

Alors ce à quoi l'obstétricien s'attend et ce après quoi il soupire, c'est d'obtenir un anesthésiste bien entraîné et expérimenté qui va lui épargner l'anxiété de penser à la tête de la malade et à son enfant pendant qu'il fait l'accouchement, qui va pratiquer promptement la ressuscitation maternelle et fœtale et qui peut surveiller la malade dans la salle de réveil. En résumé, nous demandons un ami quand nous sommes dans le besoin. Dans la grande majorité des cas, nous l'avons.

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A CIRCULATOR TO ELIMINATE MECHANICAL DEAD SPACE IN CIRCLE ABSORPTION SYSTEMS

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THE POTENCY, versatility, and usefulness of cyclopropane are acknowledged by most physicians, but the fact that for economy reasons cyclopropane is ordinarily used in a closed system has restricted its application in paediatric anaesthesia because of the important attendant disadvantages of dead space and resistance.

The desire to avoid the unpleasantness and drawbacks of frank ether and to make cyclopropane available to tiny patients led to the development of the apparatus described below. This original apparatus for the elimination of the dead space is added to ordinary equipment used in closed and semi-closed anaesthisia. The clinical application has been very rewarding and has extended over a period of ten years.

DESCRIPTION

The apparatus devised to eliminate the mechanical dead space may be referred to as a circulator since its function is to keep the gases in the under-mask space moving so that each breath as it is exhaled is carried away towards the absorber. In other words, the gases in the circle are kept in motion and the patient breathes out to and in from a passing breeze of fresh gases. This prevents the reinhalation of that part of the exhaled gases coming from the depths of the lungs which contains the highest concentration of carbon dioxide and the least oxygen.

The component parts of the device are a divided chimney-piece and a pump (Fig. 1). It is necessary to have a divided chimney-piece to produce a flow pattern that will change the gases in the under-mask space. This change is accomplished by a median septum, so that inhaled gases pass down one side and exhaled gases pass up the other. This chimney-piece is of male design and fits into the top of masks of the Heidbrink and M.I.E. pattern so that the septum can be carried right into the under-mask space. In operation the circulating pump draws gases free of carbon dioxide from the breathing bag and delivers them into the inhalation side of the circle at a point where they will force the gases along the corrugated connecting tube towards the mask. The under-mask gases are thus continuously kept moving towards the exhalation valve of the machine and thence through the absorber back to the bag.

The circulating pump is constructed from two identical suction Trico automobile windshield-wiper motors of a type in very common use. These motors are joined firmly together by their ends in such a manner that their external moving parts may also be coupled together. The two are intercoupled by a metal sling by which they are hung on and grounded to the gas machine (Fig. 2). One of these units powered by suction is operated as the motor and when in motion

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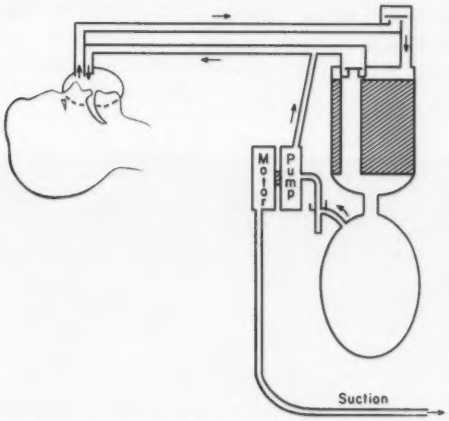

FIGURE 1. Circulator attached to circle gas machine. The motor, powered by suction, drives the pump which draws from the rebreath-bag and delivers gases into the inhalation side of the circle. A moisture condenser-trap is interposed between the bag and the pump. The circulator causes a continuous change of the gases under the mask, displacing the exhaled gases towards the absorber thus preventing reinhalation of gases containing carbon dioxide. The divided chimney-piece is essential to pattern the gas flow under the mask.

drives the other, which then becomes a pump. It is essential that the reversing mechanism of the motor be adjusted to allow the pump to execute a complete cycle in each direction. That is, the reversing mechanism of the pump must trip just before that of the motor. Making this adjustment requires an understanding of the reversing mechanism but is easily made with a file. The cover plate over the reversing parts of the pump must be fitted with a metal nipple, which becomes the intake port. All gaskets must be gas-tight on the pump. The control lever on the pump is wired in the open position while that of the motor is used to turn the motor on and off. The rate of motor operation depends on the strength of the suction available and is adjusted by a screw clamp on the rubber tube leading to the motor. The capacity of the Trico motors used is about 50 cc.; so one can calculate the volume of the gases pumped for a given rate of oscillation. It has been found that a rate of fifty cycles per minute (one hundred clicks of the reversing mechanism) will change the under-mask gases at a rate of 5 L. per minute. This has appeared clinically to be a satisfactory rate.

Owing to the high humidity of the gases pumped a condenser and water-trap is interposed between the rebreathing bag and the pump. This is cooled by the evaporation of alcohol or water poured into a small reservoir around the base of

the condenser. The pump intake nipple is connected to the breathing bag by means of a hollow bolt held in place by two plastic washers and a nut. The output of the pump is carried by a short rubber tube leading into the inhalation side of the circle just above and on the patient's side of the inhalation valve.

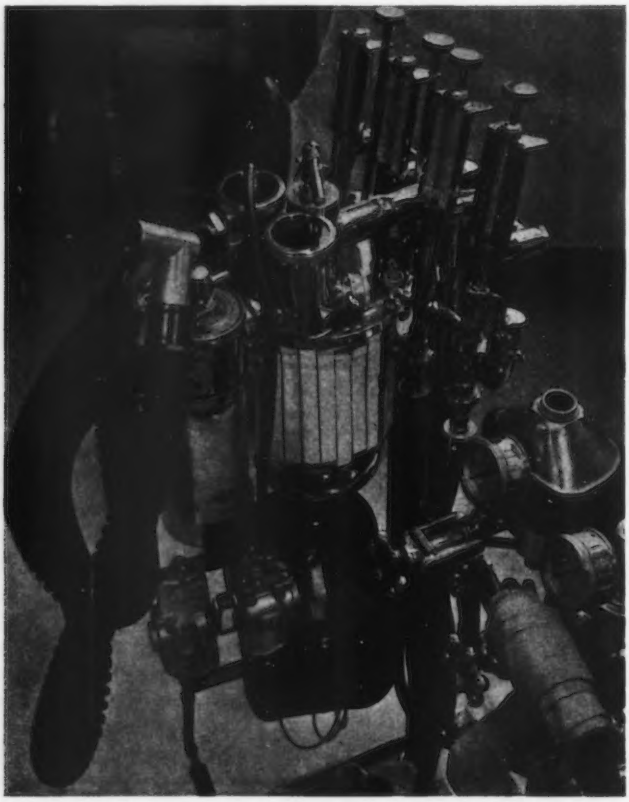

FIGURE 2. An early model of circulator attached to a Heidbrink machine. The motor-pump is suspended from the ether-jar and the rate control clip has been omitted. Note the divided chimney-piece and the moisture condenser-trap.

Since the circulator pump has a vane-type piston oscillating between two cylinders, one side is discharging its gases at the same time and rate as the other is filling. Thus the pump removes and replaces gases from and to the circle system of the anaesthetic machine without disturbing the volume or causing the breathing bag to pulsate. Therefore, the operation of the circulator does not alter the behaviour of the bag as an index of anaesthetic depth, nor is the effectiveness of the circulator interfered with by the anaesthetist assisting or augmenting respiration by intermittent compression of the bag.

Discussion

The anatomical dead space comprises the tracheobronchial tree and the upper respiratory tract. The mechanical or the anaesthetic dead space is extracorporeal and is mechanically imposed on the patient by the use of any anaesthetic equipment such as the open drop mask or the mask and connecting chimney-piece necessary to closed or semi-closed techniques. The smaller the tidal volume, the more deleterious to the patient is the imposed dead space. In small patients, and adults whose tidal volume is for any reason reduced, addition of mechanical dead space may lead to hypoxia and accumulation of carbon dioxide during anaesthesia.

The circulator allows the use of a variety of masks and reduces the need for intubation as a means of reducing dead space in many paediatric cases. Resistance to inhalation ordinarily created by the tubing and valves of the circle system is absent and exhalation is very little impeded. The slight positive under-mask pressure is an aid to inhalation, especially for very small patients. The circulator must not be confused with other recently evolved pumps or ventilators which are designed to assist with the respiratory movements of the patient, or carry out controlled respiration. The circulator is used merely to reduce the imposed dead space.

A special application of the circulator is its use to perform closed endotracheal sufflation which reduces even the anatomical dead space (Fig. 3). This has been

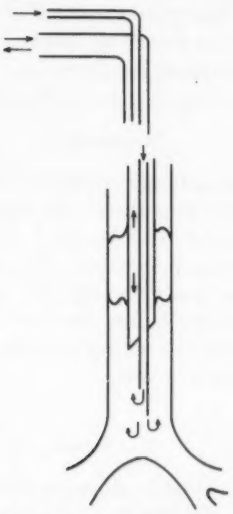

Figure 3. Set-up for closed endotracheal sufflation. The tube carrying gases from the pump is led into the endotracheal catheter at the angle adapter and extends a short distance beyond the end of the catheter. By reversing the direction of flow and connections into the circle, and interposing a liquid-catching trap, a technique of continuous closed endotracheal suction may be used. The air line to the cuff has been omitted.

done in patients undergoing open chest surgery, where it is felt that the most can be made of diffusion exchange of fresh gases introduced near the carina. This technique is not used alone, but in addition to the usual manual ventilation. Also by reversing the set-up, continuous closed endotracheal suction can be performed. The blood and pus are trapped in a small bottle and the gases are returned to the closed circle on the exhalation side. To carry out either of these techniques a thin-walled polythene tube, such as is used in disposable intravenous sets, is passed down inside the endotracheal tube to a point near the carina. This requires the use of an endotracheal adapter drilled at a point where the projected axis of the endotracheal tube meets the metal. The polythene tube should fit snugly enough to be gas-tight for ordinary pressures. The presence of the smaller tube within the larger does reduce the calibre somewhat, but plenty of room is left for adequate exchange since augmented or controlled respiration is used in these cases.

The advantages of the circulator are easily recognized in paediatric anaesthesia. It is just as logical to suggest its use also in all adult closed or semi-closed techniques for the same purpose of minimizing the ill effects of increased dead space.

In ether vaporizers which depend upon the flow of respired gases in the circle apparatus vaporization is accelerated by the additional flow provided by the circulator. This facilitates achievement of the desired level of surgical anaesthesia, but adds the danger of easily produced overdosage.

On those occasions when nitrogen is desired as a diluent to the anaesthetic mixture it can be readily added from the ambient atmosphere by momentarily opening the pump intake to the room air.

Summary

A description is given of an original apparatus for the removal of the under-mask dead space in paediatric anaesthesia. Its application to adult anaesthesia is also suggested. The apparatus may be used in conjunction with any circle closed or semi-closed absorption technique. The principle of operation is the forcing of carbon dioxide free gases through the under-mask space in order to displace the exhaled atmosphere before the next inhalation takes place. The technique has been used in all the writer's paediatric cases since 1947 and in those of his associates in the last five years.

Addendum

The author is aware that a double chimney-piece and a hand-operated bulb pump have been described in the literature in recent years. The author's divided chimney-piece which has been in use for more than ten years was sent to the Heidbrink Division of the Ohio Chemical Company in Madison, Wisconsin, in 1947, and its use explained as a means of reducing the dead space in conventional chimney-pieces. A chimney-piece of this exact design is now available from Heidbrink. The use of the circulator and its development were presented in a

formal paper to the British Columbia Division of the Canadian Anaesthetists' Society in Victoria in 1949 and again before the Pacific Northwest Society of Anesthetists at Portland, Oregon, in September, 1950. Though not on the programme, the circulator was shown in the commercial exhibits at the Western Regional Conference in San Francisco in March 1949.

Résumé

Nous avons décrit un appareil original qui peut être utilisé en anesthésie lorsque l'on se sert d'un circuit fermé ou semi-fermé avec absorption. L'usage de cet appareil a pour effet d'éliminer l'espace mort mécanique inévitable en activant continuellement la circulation des gaz inspirés. L'usage d'une pompe à succion et d'un tube connecteur à deux branches maintiennent en circulation les gaz dans le circuit, les diluant et enlevant du masque les gaz exhalés avant l'inhalation suivante. Ceci diminue l'importance du petit volume d'air courant des enfants et permet l'usage de l'outillage pour adultes avec toute sécurité dans les cas de pédiâtrie. Cet appareil est sans fantaisie et ne comporte pas les risques d'explosion que cachent les appareils électriques. Sa grande valeur est de permettre l'usage d'une technique fermée et semi-fermée sans espace mort additionnel. L'appareil, avec un ajustement spécial, rend possible l'insufflation endotrachéale continue ou la succion dans un circuit fermé, système qui peut être pratique dans certains cas de chirurgie pulmonaire. Il ne s'agit pas d'un ventilateur mécanique mais d'un circulateur qui réduit la supposée accumulation de gaz carbonique en changeant continuellement les gaz dans le masque. Nous employons cette technique depuis dix ans. Parmi les nombreux cas où cet appareil a servi, nous comptons des nouveaux-nés pesant aussi peu que quatre livres.

AN IMPROVED CIRCULATOR FOR CLOSED CIRCLE ANAESTHESIA

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A PREVIOUS PAPER described a circulator for the elimination of dead space in closed and semi-closed absorption systems (1). A simpler, more convenient method of propelling the anaesthetic gases around the circle absorber has been developed. This method also employs the divided chimney-piece to lead the gases down into and away from the under-mask space. The pump employed to impel the gases is of simple design and is conveniently inserted or included into the circle system at the point where the inhaling connecting tube leaves the absorber head. This circulator is better than the oscillating type in that it moves *all* the gases continuously in the circle, and a moisture condenser-trap with additional taps into the bag and the circle is unnecessary. Thus it may be attached to the gas machine in a matter of seconds.

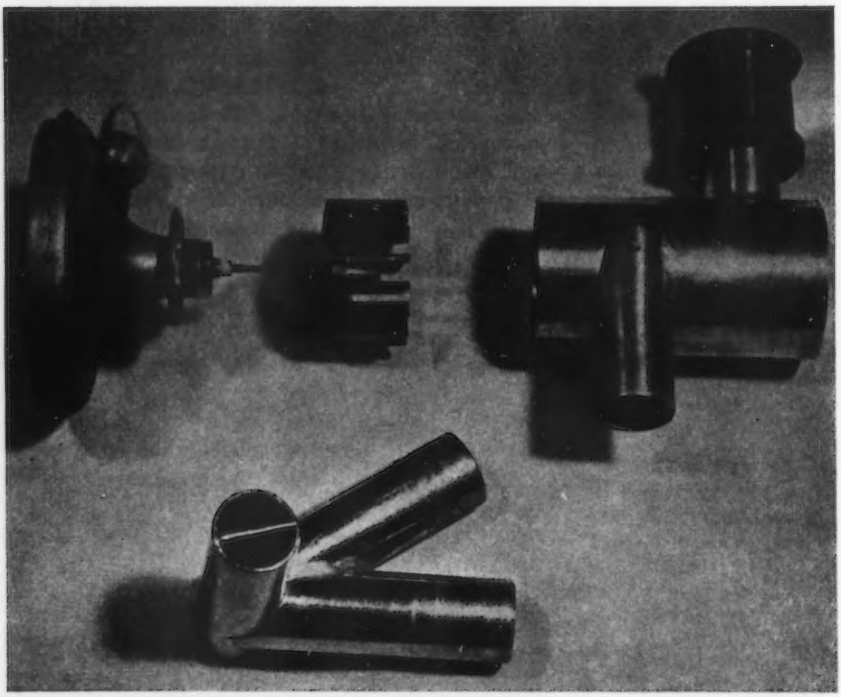

FIGURE 1. Disassembled total circulator for the elimination of under-mask dead space. *Upper left* is the suction-powered turbine motor (Trico); *centre*, plastic impeller, which threads onto shaft of motor inside the cylindrical housing, *right*. The ends of the housing are closed except where the shaft of the motor is mounted. *Below* is the divided chimney-piece without which the under-mask gases would not be circulated.

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This circulator may be described as a turbo-impeller (Fig. 1). It consists of two rotating parts on a common shaft. One rotating part is the turbine-type motor powered by suction, or in reality by atmospheric air pressure. This little motor comes as the main part of the Trico automobile fan which is designed for mounting near the windshield to prevent condensation on the inside of the glass. The other rotating part is a polythene plastic squirrel-wheel type of air-mover found in a push-button electric plant-duster made by the E. C. Brown Co. at Canandaigua, N.Y. This neat spindle-shaped air-mover happens to be threaded the proper size to fit onto the shaft of the Trico motor.

The housing of the circulator is made of brass tubing of 1¾ in. inside diameter. The motor is mounted on one end of a 3 in. cylinder of this tubing, so that the shaft is inside and in line with the axis of the cylinder. The squirrel-wheel fits into the cylinder and is mounted by threading onto the shaft of the motor. This can now be made to spin inside the brass cylinder, and with the proper placing of tubular ports becomes an effective pump. The other end of the brass cylinder is closed with a removable plug. Maintenance is very simple as the small shaft is lubricated with graphite oil and is air-cooled when in operation.

When used in a Heidbrink circle, the original metal-rubber valve disks are replaced by very light plastic disks. These are so light that at quite moderate operation speed this new circulator causes them to stand open during all phases of the respiratory cycle. It would not harm the effectiveness of the circulator if either valve were to seat momentarily at the peak respiratory flow caused by the patient during either inhalation or exhalation, or both, as long as they are open during the pause before inhalation. It is during this latter interval that the just exhaled gases are swept away towards the absorber by fresh gases from the bag.

When mounted ready for use, the intake port is connected to the inhalation outlet of the absorber head by a rubber nipple and the connecting tube leads from the outlet of the circulator to the divided chimney-piece on the mask (Fig. 2). In operation, after a gas-tight fit of the mask on the face has been made, the suction line to the motor is opened by a screw clip and the rate adjusted so that the valves of the gas machine are made to float open. This of course means that the gases are circulating, and the valves will be seen to move slightly with the inspirations and exhalations of the patient. The action of this pump raises the under-mask pressure by about 2 mm. of water above the pressure in the whole system. This in no way interferes with the respiratory movements of even the smallest patient but does relieve the patient from having to lift the inhalation valve or overcome the inertia of the gases with each inhalation.

In order that the gases will not be passed through the soda lime too rapidly, the circulator should be run at the slowest rate at which the valve disks can be kept floating, though it does not matter if they become seated momentarily at the height of respiratory gas movements. Without circulation the gases dwell in the soda-lime chamber either during inhalation or during exhalation depending on which side of the circle the absorber is located. With circulation this pause is absent, but absorption is quite adequate as the gases pass through the soda lime many more times per minute than otherwise. No clinical signs of carbon dioxide accumulation have been observed during the use of circulated closed technique in hundreds of paediatric and adult patients.

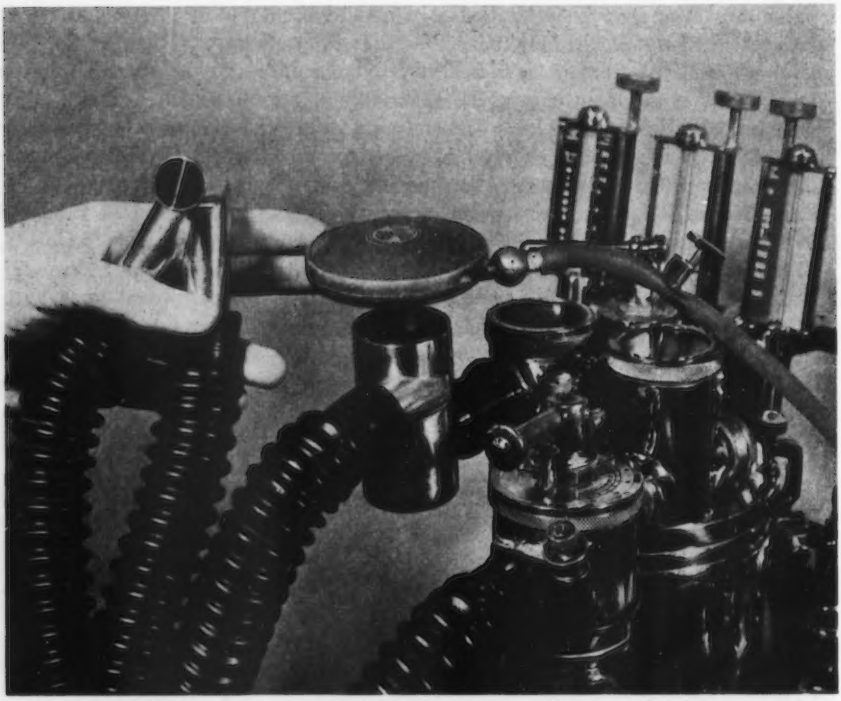

FIGURE 2. Vacuum turbine-powered circulator in place on a Heidbrink absorber head. This circulator moves all the gases in the system at such a rate that they pass through the soda lime many times in a minute, ensuring repeated opportunities for carbon dioxide absorption. Lightweight valve disks have been placed in the absorber head. The circulator is set to operate at a rate which just keeps these valves open. The rate of operation is dependent upon the degree of suction available and the adjustment of the screw clamp shown on the suction line leading to the motor. The divided chimney-piece patterns the under-mask gas flow to provide continuous change.

One effect of circulation in a closed system must be kept in mind. The usual Heidbrink wick-type ether vaporizer operates by having fractional amounts of the exhaled gases pass through the ether chamber. Thus ether vapour is picked up only when the respired gases pass around the circle as a result of the patient's respiratory effort or as a consequence of manual assistance by the anaesthetist, and etherization is therefore dependent on the minute volume. However, with the circulator propelling the gases continuously around, much more ether vapour can be added to the system per unit time. This is actually found to be an advantage since deep ether anaesthesia may be accomplished quite quickly with the circulator in operation. One soon learns to set the vaporizer control at a small opening to avoid too rapid increase in concentration.

Carefully controlled clinical studies have been made in which endotracheal carbon dioxide concentrations have been continuously recorded during anaes-

thesia. Arterial blood specimens taken prior to and during use of the circulator have shown satisfactory levels of blood plasma pH and CO_2.

A prototype of this circulator has been in clinical use for five years with very satisfactory results in all sizes of paediatric patients. As cyclopropane is such a versatile and satisfactory agent for anaesthesia in babies and children, the use of a circulator allows the use of this agent with any adult circle absorption machine with light valves. Circulation may be used in closed or semi-closed techniques, and it obviates the need for high flow rates or semi-open techniques as a means of minimizing dead space.

The illustrations show the circulator both disarticulated and assembled in place on the gas machine. The divided chimney-piece—an essential part of the apparatus—is to be noted.

Summary

A vaccuum-powered turbo-impeller is described for use in closed or semi-closed anaesthetic techniques. Use of this apparatus with a divided chimney-piece eliminates the under-mask dead space and permits the safe use of cyclopropane and ether in a closed system for paediatric anaesthesia.

Acknowledgment

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Résumé

Nous avons décrit un circulateur amélioré à turbine pour éliminer l'espace mort sous le masque. Ce circulateur, plus simple, plus silencieux, fonctionne par succion, se fixe facilement et rapidement à n'importe quelle machine à gaz, requérant seulement que les valves soient un matériel très léger. Au moyen d'un connecteur divisé appliqué sur le masque, la circulation des gaz engendre sous le masque un courant d'air qui emporte l'air exhalé et le remplace par le l'air frais venant de la machine. Ce circulateur, plusieurs fois à la minute, fait faire le tour du circuit à l'atmosphère qu'il contient, y compris à travers l'absorbeur. De plus, il facilite considérablement l'évaporation de l'éther ou de tout autre agent liquide lorsque cet agent est ajouté aux mélanges cyclopropane, protoxyde et oxygène.

REFERENCE

1. Revell, D. G. A Circulator to Eliminate Mechanical Dead Space in Circle Absorption Systems. Canad. Anaesth. Soc. J. *6*: 98–103 (April, 1959).

A CLINICAL COMPARISON OF SODIUM THIOPENTAL (PENTOTHAL®), SODIUM METHITURAL (NERAVAL®), SODIUM BUTHALITONE (TRANSITHAL®), AND SODIUM HEXOBARBITAL (EVIPAL®)

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MUCH HAS been written in recent years of the relative advantages and disadvantages of new intravenous anaesthetics. Such comparisons are always difficult to make because of the many variables which cannot be easily controlled in a clinical series. For that reason, we attempted some time ago to compare a number of intravenous agents in human volunteers, administering each drug consecutively to the same individuals under rigidly controlled conditions (1, 2). Double the sleep dose of each drug was given in a standard concentration and at a standard rate. For a variety of reasons the results obtained did not necessarily reflect each agent's usefulness in clinical practice. The standardization of concentration is a procedure open to criticism. Also, it is very difficult to determine equi-potent doses for each agent and the administration of double the sleep dose is not an exact criterion since the sleep dose itself is hard to define. It was felt that a further controlled study should be undertaken, restricting the administration of each agent to patients undergoing a standard operative procedure and using as the criterion of dosage the amount of drug required to permit the performance of the operation. The concentrations used in this study were the ones commonly employed in the clinical use of these agents.

It was hoped that the present clinical study would yield additional information which would enhance the value of our previous experimental results when considered side by side with them.

METHOD

As in previous clinical studies of intravenous anaesthetics (3, 4) the drugs were administered for minor gynaecological procedures only and their use was limited to patients in physical status 1 and 2. Freshly prepared 2½ per cent solutions of thiopental and methitural and 10 per cent solutions of buthalitone and hexobarbital were used. These concentrations are the ones used commonly in clinical practice. Anaesthesia was maintained by intermittent injection. The patients received oxygen by mask in a semi-closed system at a flow of 6 L. per minute. Muscle relaxants were given only when muscle relaxation for pelvic examination was inadequate. All patients were premedicated with meperidine 50 mg. and atropine 0.4 mg. intramuscularly. Fifty patients were studied in each series. Each drug was compared with thiopental and a further comparison was

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made between methitural and buthalitone because these two agents are said to have some properties in common. Hence the methitural series is included in the present study although it has been published previously (3).

Discussion of Results

Age, height, and weight (Tables I and II). Differences in the four comparisons were statistically not significant. Hence, the four groups are comparable as far as age, height, and weight are concerned.

TABLE I

Age

	Oldest (yrs.)	Youngest (yrs.)	Mean (yrs.)	(mo.)	S.D.
Thiopental	69	12	36	3	11.81
Methitural	72	16	34	9	10.90
Buthalitone	62	17	35	9	11.64
Hexobarbital	65	19	34	4	12.06

Comparisons: Thiopental/Methitural, $t = 0.677$; Thiopental/Buthalitone, $t = 0.230$; Thiopental/Hexobarbital, $t = .803$; Methitural/Buthalitone, $t = -0.442$.

S.D. = Standard Deviation.

TABLE II

Height and Weight

	Mean Height (in.)	S.D.*	Mean weight (lb.)	S.D.
Thiopental	63.10	2.16	136.52	24.48
Methitural	63.10	2.31	129.69	23.64
Buthalitone	63.67	2.65	133.31	25.79
Hexobarbital	63.30	2.58	130.47	18.47

S.D. = Standard Deviation.

Comparisons

Thiopental/Methitural	$t = 0$	$t = -1.211$
Thiopental/Buthalitone	$t = -1.180$	$t = 0.638$
Thiopental/Hexobarbital	$t = -.379$	$t = 1.394$
Methitural/Buthalitone	$t = -1.145$	$t = -0.734$

Time from premedication to induction of anaesthesia (Table III). There was the usual wide variation in the time from premedication to induction. Only in the comparison of thiopental with methitural is the difference of the mean

TABLE III

Time from Premedication to Induction

	Longest (hr.)	(min.)	Shortest (min.)	Mean (hr.)	(min.)	S.D.
Thiopental	2	49	2	1	20	28.94
Methitural	3	20	34	1	25	29.58
Buthalitone	3	27	0	1	38	32.05
Hexobarbital	2	41	40½	1	32	29.73

Comparisons: Thiopental/Methitural, $t = -0.806$; Thiopental/Buthalitone, $t = -2.908$**; Thiopental/Hexobarbital, $t = -2.035$*; Methitural/Buthalitone, $t = -2.117$*.

S.D. = Standard Deviation.

*Sig. (Significant) ($P < .05$).

**H.S. (Highly Significant) ($P < .01$).

statistically not significant. Standardization of this variable has been found impossible under operating-room conditions.

Duration of anaesthesia and operation (Tables IV and V). Significant or almost significant differences were apparent in the thiopental-methitural and thiopental-buthalitone comparisons only. In the comparisons between thiopental and hexobarbital and between methitural and buthalitone, no such significant differences existed.

TABLE IV

DURATION OF ANAESTHESIA

	Longest (min.)	Shortest (min.)	Mean (min.)	(sec.)	S.D.
Thiopental	29	5	18	19	5.42
Methitural	28	4	15	2½	4.49
Buthalitone	33	7	16	14	5.31
Hexobarbital	33	9	19	23	6.15

Comparisons: Thiopental/Methitural, $t = 3.284$**; Thiopental/Buthalitone, $t = 1.929$†; Thiopental/Hexobarbital, $t = -.931$; Methitural/Buthalitone, $t = -1.224$.

S.D. = Standard Deviation.
**H.S. ($P < .01$).
†Almost, but not quite significant.

TABLE V

DURATION OF OPERATION

	Longest (min.)	Shortest (min.)	Mean (min.)	(sec.)	S.D.
Thiopental	27	2	12	40	5.26
Methitural	23	4	9	41	4.26
Buthalitone	30	2	10	18	4.75
Hexobarbital	25	3½	11	46	5.35

Comparisons: Thiopental/Methitural, $t = 3.088$**; Thiopental/Buthalitone, $t = 2.370$*; Thiopental/Hexobarbital, $t = .840$; Methitural/Buthalitone, $t = -0.667$.

S.D. = Standard Deviation.
*Sig. ($P < .05$).
**H.S. ($P < .01$).

Total anaesthetic dose (Table VI). The differences in all four comparisons were statistically highly significant.

TABLE VI

TOTAL ANAESTHETIC DOSE

	Maximum (mg.)	Minimum (mg.)	Mean (mg.)	S.D.
Thiopental	1,000	250	585.5	146.39
Methitural	1,500	625	1,021	206.50
Buthalitone	2,100	800	1,498.4	352.78
Hexobarbital	3,000	900	1,528	471.34

Comparisons: Thiopental/Methitural, $t = -12.183$**; Thiopental/Buthalitone, $t = -16.899$**; Thiopental/Hexobarbital, $t = -13.503$**; Methitural/Buthalitone, $t = -8.262$**.

S.D. = Standard Deviation.
**H.S. ($P < .01$).

Induction and maintenance doses (Tables VII and VIII). Significant differences existed in all four comparisons as far as the induction dose was concerned. The differences in the maintenance dose were statistically significant for the three comparisons with sodium thiopental, but the difference of the mean maintenance dose of buthalitone as compared with methitural was not significant.

TABLE VII

INDUCTION DOSE

	Maximum (mg.)	Minimum (mg.)	Mean (mg.)	S.D.
Thiopental	250	75	244	30.12
Methitural	500	375	385	34.24
Buthalitone	1,000	450	521	86.95
Hexobarbital	700	500	522	54.55

Comparisons: Thiopental/Methitural, $t = -21.933$**; Thiopental/Buthalitone, $t = -21.291$**; Thiopental/Hexobarbital, $t = -31.556$**; Methitural/Buthalitone, $t = -10.287$**.

S.D. = Standard Deviation.
**H.S. ($P < .01$).

TABLE VIII

MAINTENANCE DOSE

	Maximum (mg.)	Minimum (mg.)	Mean (mg.)	S.D.
Thiopental	750	0	341.5	147.74
Methitural	1,125	250	636	206.84
Buthalitone	1,600	300	977	356.21
Hexobarbital	2,300	400	1,006	447.51

Comparisons: Thiopental/Methitural, $t = -8.192$**; Thiopental/Buthalitone, $t = -11.659$**; Thiopental/Hexobarbital, $t = 9.977$**; Methitural/Buthalitone, $t = -0.586$.

S.D. = Standard Deviation.
**H.S. ($P < .01$).

Dose per minute of anaesthesia (Table IX). Because of the significant difference in the mean duration of anaesthesia in the thiopental-methitural comparison and the almost significant difference in the thiopental-buthalitone

TABLE IX

DOSE PER MINUTE OF ANAESTHESIA

	Mean (mg.)	S.D.
Thiopental	34.91	15.14
Methitural	72.25	20.43
Buthalitone	98.06	27.89
Hexobarbital	84.92	33.62

Comparisons: Thiopental / Methitural, $t = -10.384$**; Thiopental/Buthalitone, $t = -14.065$**; Thiopental/Hexobarbital, $t = -9.580$**; Methitural/Buthalitone, $t = -5.278$**.

S.D. = Standard Deviation.
**H.S. ($P < .01$)

comparison, the dose required per minute of anaesthesia was calculated. The differences in all four comparisons were highly significant. They indicated that thiopental was about twice as potent as any of the other three with methitural, hexobarbital, and buthalitone fairly close together in order of decreasing potency.

Total sleep time (Table X). This was defined as the time between induction of anaesthesia and the patient's purposeful response to verbal command. The differences in the thiopental-hexobarbital comparisons were statistically highly significant whereas the remaining three comparisons were not significant. This indicates that for a standard operative procedure there is no difference in the sleep time after thiopental, methitural, or buthalitone, whereas awakening following hexobarbital anaesthesia is greatly delayed.

TABLE X

TOTAL SLEEP TIME

	Longest (hr.)	Longest (min.)	Shortest (min.)	Mean (min.)	Mean (sec.)	S.D.
Thiopental	1	35	9	44	11	21.05
Methitural	1	10	23	40	12	12.24
Buthalitone	1	56	10	45	49	26.77
Hexobarbital	3	40	21	89	38	46.90

Comparisons: Thiopental/Methitural, $t = 1.155$; Thiopental/Buthalitone, $t = -0.340$; Thiopental/Hexobarbital, $t = -6.252$**; Methitural/Buthalitone, $t = -1.351$.

S.D. = Standard Deviation.

**H.S. ($P < .01$).

Waking time from last injection (Table XI). This was the period from the last injection until the time when the patient responded to verbal command. Again, differences were statistically significant only in the thiopental-hexobarbital comparison and it is, therefore, concluded that hexobarbital has the longest action of the four agents studied. The other three agents have a very similar duration of action under the conditions of this study.

TABLE XI

WAKING TIME FROM LAST INJECTION

	Longest (hr.)	Longest (min.)	Shortest (min.)	Mean (min.)	Mean (sec.)	S.D.
Thiopental	1	25	7	31	49	18.90
Methitural	—	55	9	30	28	11.34
Buthalitone	1	39	5	33	16	25.20
Hexobarbital	3	32½	10	75		47.23

Comparisons: Thiopental/Methitural, $t = -0.436$; Thiopental/Buthalitone, $t = -0.326$; Thiopental/Hexobarbital, $t = -5.997$**; Methitural/Buthalitone, $t = -0.719$.

S.D. = Standard Deviation.

**H.S. ($P < .01$).

Dose per minute of sleep time (Table XII). The differences in all four comparisons were statistically highly significant. Because of the prolonged sleep

after hexobarbital, the sequence here is thiopental, hexobarbital, methitural, buthalitone.

TABLE XII

DOSE PER MINUTE SLEEP TIME

	Mean (mg.)	S.D.
Thiopental	15.57	9.72
Methitural	26.97	7.05
Buthalitone	42.74	20.82
Hexobarbital	20.54	9.58

Comparisons: Thiopental / Methitural, $t = -6.709^{**}$; Thiopental/Buthalitone, $t = -8.360^{**}$; Thiopental/Hexobarbital, $t = -2.576^{**}$; Methitural/Buthalitone, $t = -5.071^{**}$.

S.D. = Standard Deviation.
**H.S. ($P < .01$).

Side effects (Table XIII). There was no significant difference between the incidence of *cough* in the thiopental-buthalitone and thiopental-hexobarbital comparisons. With methitural, the incidence during induction and maintenance was significantly higher than with either of the other three agents.

On the other hand the incidence of *hiccough* was greatest with buthalitone. There was no significant statistical difference between thiopental and methitural. With hexobarbital, hiccough was rare.

TABLE XIII

SIDE EFFECTS

	Cough incidence (%)	S.D.	Hiccough incidence (%)	S.D.	Movements incidence (%)	S.D.
Thiopental	6	.03	12	.05	76	.06
Methitural	22	.06	24	.06	86	.05
Buthalitone	8	.04	50	.07	72	.06
Hexobarbital	2	.02	2	.02	100	.00
Comparisons						
Thiopental/Methitural	$t = -2.366^{**}$		$t = -1.581$		$t = -1.282$	
Thiopental/Buthalitone	$t = -0.392$		$t = -4.524^{**}$		$t = 0.455$	
Thiopental/Hexobarbital	$t = 1.026$		$t = 2.000^{*}$		$t = 4.000^{**}$	
Methitural/Buthalitone	$t = 2.000^{*}$		$t = -2.796^{**}$		$t = 1.750$	

S. D. = Standard Deviation.
*Sig. ($P < .05$).
**H.S. ($P < .01$).

Movements occurred in many patients in all three groups. This was because slight movements were used as an indication for additional amounts of drug and may, therefore, be ignored for purposes of evaluation. Movements involving the legs to the point where such movements were noticed by the surgeon were

classified as moderate. Gross movements involved the entire body and included withdrawal of the pelvis. No such moderate or gross movements were seen under thiopental anaesthesia, but there was a significant incidence of these with both buthalitone and methitural, and they occurred in the majority of patients receiving hexobarbital (Table XIV). These severe movements could not always be adequately controlled by increasing the dose of the drug.

TABLE XIV
MOVEMENTS

	None	Slight	Moderate	Severe
Thiopental	12 (24%)	38 (76%)	0	0
Methitural	7 (14%)	34 (68%)	5 (10%)	4 (8%)
Buthalitone	15 (30%)	29 (58%)	3 (6%)	3 (6%)
Hexobarbital	— (0%)	13 (26%)	32 (64%)	5 (10%)

Apnoea (Table XV). The *incidence* of apnoea following an induction dose of thiopental was very high, significantly less so with methitural, even less so with buthalitone and least with hexobarbital. A similar relation applied to the mean *duration* of apnoea; this was longest with thiopental and shortest with hexobarbital.

TABLE XV
APNOEA

	Incidence	S.D.	Longest (sec.)	Shortest (sec.)	Mean (sec.)	S.D.
Thiopental	94% (47)	.03	120	10	40.1	25.90
Methitural	58% (29)	.07	70	1	21.2	23.62
Buthalitone	38% (19)	.07	120	5	11.8	22.03
Hexobarbital	22% (11)	.06	55	10	5.0	11.02

Comparisons

Thiopental/Methitural	$t = 4.622^{**}$	$t = 3.808^{**}$
Thiopental/Buthalitone	$t = 7.368^{**}$	$t = 5.884^{**}$
Thiopental/Hexobarbital	$t = 10.746^{**}$	$t = 8.841^{**}$
Methitural/Buthalitone	$t = 2.041^{*}$	$t = 2.061^{*}$

S.D. = Standard Deviation.
*Sig. ($P < .05$).
**H.S. ($P < .01$).

Relaxants (Table XVI). Small doses of succinylcholine were given whenever muscular relaxation was inadequate for proper bimanual pelvic examination. From the analysis of the data, it would appear that both methitural and hexobarbital tend to relax slightly the lower abdominal muscles since relaxants were infrequently needed with these two drugs. The differences between them and thiopental were significant. The difference between thiopental and buthalitone was statistically not significant.

TABLE XVI

RELAXANTS

		S.D.
Thiopental	34% (17)	.07
Methitural	8% (4)	.04
Buthalitone	24% (12)	.06
Hexobarbital	4% (2)	.03

Comparisons: Thiopental/Methitural, $t = 3.377^{**}$; Thiopental/Buthalitone, $t = 1.562$; Thiopental/Hexobarbital, $t = 4.167^{**}$; Methitural/Buthalitone, $t = -3.137^{**}$.

S.D. = Standard Deviation.
**H.S. ($P < .01$).

Emergence from anaesthesia (Table XVII). *Hiccough* was entirely absent after buthalitone, thiopental, and hexobarbital, but was relatively common after methitural. On the other hand, the incidence of *nausea and vomiting* was very high after hexobarbital. They occurred much less frequently following administration of the other three agents, with thiopental causing these reactions somewhat more frequently than the remaining two drugs.

TABLE XVII

EMERGENCE

	Depression and drowsiness	Restlessness	Emotional upset	Dizziness	Coughing	Hiccough	Vomiting and retching	Hypotension
Thiopental	1	—	—	1	—	—	5	—
Methitural	1	1	—	—	1	6	2	—
Buthalitone	—	—	—	—	—	—	3	—
Hexobarbital	—	1	1	—	—	—	21	1

Recovery period (Table XVIII). The incidence of post-anaesthetic *nausea and emesis* was relatively high after hexobarbital, lasting frequently as long as twelve hours. Three patients each experienced *vertigo and headache* following the drug. Two patients complained of headache following buthalitone and six others had vertigo. *Drowsiness and tiredness* were complained of by a small number of patients after thiopental, methitural, and buthalitone.

TABLE XVIII

RECOVERY PERIOD

	Irrational behaviour	Drowsiness and tiredness	Headache	Dizziness	Nausea and retching
Thiopental	—	1	—	2	—
Methitural	—	3	—	2	—
Buthalitone	—	2	2	6	—
Hexobarbital	1	—	3	3	7

Summary

The claim that some of the newer barbiturates have a shorter duration than older agents has not been borne out by the present investigation in regard to thiopental, but is true in regard to sodium hexobarbital. If sodium thiopental, sodium buthalitone, or sodium methitural is used as the sole agent for a standard operative procedure, the least amount which will keep the patient quiet on the table being administered, there is no difference in the total sleep time or in the waking time from the last injection.

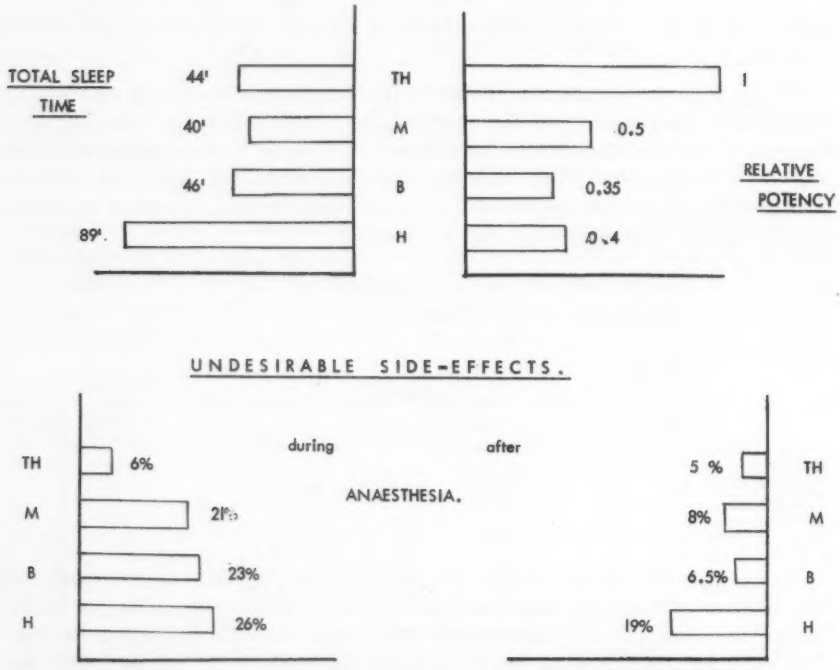

FIGURE 1. TH : Thiopental; M : Methitural; B : Buthalitone; H : Hexobarbital.

If dose per minute of anaesthesia for such a standard procedure is taken as an indication, the relative *potency* of the four agents studied is: thiopental, 1; methitural, 0.5; hexobarbital, 0.4; and buthalitone, 0.35. The most potent agent shows the highest incidence of apnoea following induction and the longest mean duration of apnoea; the less potent ones have a lower incidence and a shorter mean duration of apnoea.

The incidence of *cough* during induction and maintenance is very much greater with methitural than with the other three drugs, whereas the incidence of hiccough during maintenance is much greater with buthalitone than with the

other three drugs. The incidence of moderate and gross *movements* following sodium hexobarbital is very high indeed. Sodium thiopental appears the most predictable and reliable of the four drugs, and it is invariably possible to control slight movements of patients and thus maintain smooth anaesthesia. With the other three drugs this is not always possible, and with sodium hexobarbital it is rarely possible, even when the amount of drug administered is markedly increased. Sodium methitural and sodium hexobarbital are the only ones which seem to *relax* abdominal muscles slightly. This action reduces the need for relaxants for bimanual pelvic examination considerably compared with the other two drugs.

In the post-anaesthetic period *hiccough* is again a relatively frequent phenomenon after methitural anaesthesia and *nausea and vomiting* are very common following hexobarbital. After buthalitone and hexobarbital *dizziness and headache* are more frequently seen than after the other two agents.

In summary, it appears that sufficiently large doses of the inherently shorter-acting methitural and buthalitone are required for smooth anaesthesia, so that total sleep time is in the end no different from thiopental. Anaesthesia is neither as smooth nor as predictable and free from annoying minor side effects as it is when thiopental is used. These disadvantages outweigh the shorter post-induction apnoea with methitural and buthalitone. The very high incidence of movements during anaesthesia, the long postoperative sleep and the high incidence of nausea and emesis in the post-anaesthetic period far outweigh the low incidence and duration of post-induction apnoea following sodium hexobarbital anaesthesia.

Acknowledgments

Statistics were done by Dr. N. Shklov, Department of Mathematics, University of Saskatchewan. The authors are indebted to the members of the Department of Obstetrics and Gynaecology, whose patients were used for this study.

Résumé

Nous avons administré, en doses fractionnées, à cinquante femmes en santé qui devaient subir des opérations gynécologiques mineures, du thiopenthal de sodium (Pentothal®), du methitural de sodium (Neraval®), du buthalitone de sodium (Transithal®) et de l'hexobarbital de sodium (Evipal®). Nous avons comparé le methitural de sodium, le buthalitone de sodium et l'hexobarbital de sodium avec le thiopental de sodium et le methitural de sodium avec le buthalitone de sodium. Nous avons employé des solutions à 2½% pour le thiopental et le methitural et des solutions à 10% pour le buthalitone et l'hexobarbital. Nous avons observé que, pour une opération ordinaire régulière, si nous employons, comme seul agent, le thiopental, le buthalitone ou le methitural, la durée totale du sommeil pour chacun des agents était la même. Après l'emploi de l'hexobarbital, la durée du sommeil est beaucoup plus longue. Le pouvoir relatif des trois agents est: le thiopental, 1; le methitural, 0.5; l'hexobarbital, 0.4;

et le buthalitone, 0.35. En ce qui concerne l'apparition et la durée d'apnée, le thiopental se classe premier et l'hexobarbital dernier. Le plus fiable des quatre agents étudiés a été le thiopental; nous avons réussi avec lui à maintenir une douce anesthésie, ce que nous ne pouvons pas dire des trois autres. Nous avons noté de la toux plus souvent avec le methitural qu'avec les deux autres agents, du hoquet plus souvent avec le buthalitone et des mouvements de toute amplitude durant l'anesthésie à l'hexobarbital. Nous avons observé un léger effet myorésolutif sur les muscles de l'abdomen inférieur avec le methitural et l'hexobarbital de sodium et non pas avec le thiopental et le buthalitone. Après l'anesthésie, le hoquet est relativement plus fréquent avec le methitural et, après l'hexobarbital, il y a plus de nausées et de vomissements. Après le buthalitone et l'hexobarbital, nous avons observé très souvent de la céphalée et des étourdissements.

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THE EFFECT OF ANTICHOLINERGIC DRUGS ON THE CARDIAC VAGUS:[1] II, THE CARDIOVASCULAR RESPONSE OF ANIMALS TO ELECTROCONVULSIVE THERAPY[2]

ALLEN B. DOBKIN, M.D., and JERZY OLSZEWSKI, M.D.[3]

THE EFFECT of electroconvulsive therapy (ECT) in man poses a number of questions which cannot be answered unequivocally, because the convulsion interferes with the clinical observation of physical signs (palpation of the pulse and auscultation of the heart), and the current generated by the electrical stimulator produces a disturbance in the electrocardiograph recorder. The electrocardiograph tracing is obscured further by action currents from skeletal muscles, particularly during the clonic phase of the convulsion.

The following experiments were carried out on animals in order to observe directly the effect of unmodified ECT on the heart and circulatory dynamics. The effect of modifying ECT with thiopental or with succinylcholine and the role which the vagus nerves and anticholinergic drugs may play in modifying cardiac action during such therapy were also studied. This information was sought to supplement observations made during clinical investigations on mental patients undergoing ECT (1).

MATERIALS AND METHODS

Direct observations were made first on two rabbits under pentobarbital anaesthesia. Respiration was controlled with an intermittent positive pressure (I.P.P.) pump connected to a tracheotomy tube in order to eliminate the effects of hypoxia and hypercarbia. The heart was viewed through a bilateral thoracotomy. After removing the pericardium, silver–silver chloride electrodes were applied to the anterior and posterior aspects of the heart. The ECG was recorded on a direct-writing Sanborn Visocardiette. Electric shocks of various intensities and durations were applied to the head and to other regions of the body of the rabbit through needle electrodes.

Multiple experiments were carried out then on fifteen mongrel dogs weighing 14 to 44 lb.: before and after cold blocking and electrical stimulation of the vagus nerves; before and after the intravenous administration of thiopental or succinylcholine; and before and after the intravenous administration of anticholinergic drugs (atropine, scopolamine, oxyphenonium, and hexocyclium) or

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sectioning of the vagus nerves. The following animals and preparations were used (Fig. 1):

In four dogs under pentobarbital anaesthesia, respiration was controlled by an I.P.P. ventilator with compressed air or oxygen delivered through an endotracheal tube. Bilateral thoracotomy and pericardectomy were performed to expose the heart and

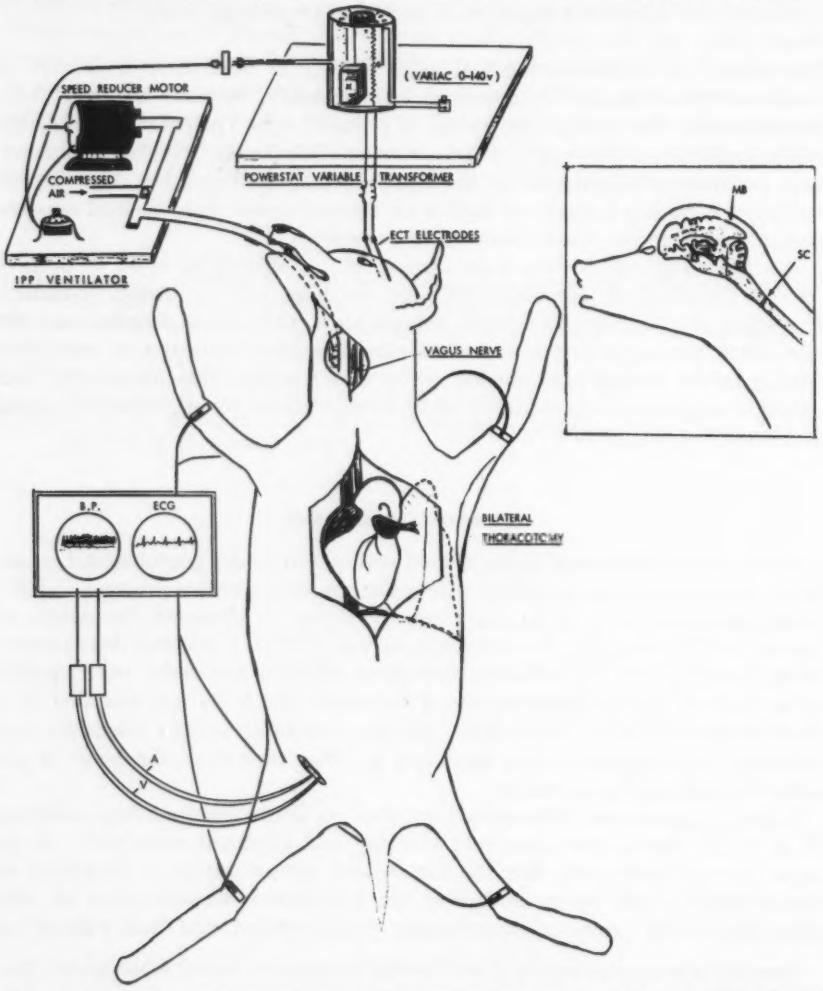

FIGURE 1. Experimental arrangement for observation of the effect of ECT and vagal stimulation on the heart, the blood pressures (aorta and inferior vena cava), and the electrocardiogram. Insert shows where central nervous system was interrupted in order to remove non-specific ascending and descending motor and sensory impulses which would complicate the visceral response to ECT when no chemical anaesthesia was desired. A signal light joined the shocking switch to the margin of the thoracotomy to indicate the time when current was flowing (not shown in diagram).

great vessels. Blood pressures in the aorta and the inferior vena cava were recorded through eighteen-gauge plastic catheters inserted through the femoral artery and vein and attached to Statham strain gauges, or to a rotating drum kymograph. ECG lead 2 and blood pressures were recorded simultaneously on a multi-channel oscilloscope and photographic recorder. The ECG was recorded also on a Sanborn direct-writing Visocardiette. ECT was provided by a powerstat variable transformer (variac 0–140 volts) through needle electrodes.

In three dogs under ether anaesthesia the spinal cord was divided at the level of the second cervical vertebra by a laminectomy and the dog was allowed to recover. The cervical vagi were then exposed to study the effect of direct stimulation and the effect of ECT after cold block and section of the vagi. Otherwise the preparations, experiments, and recordings were the same as above.

In eight dogs under ether anaesthesia, a mid-brain section was made through burr-holes in the skull. The dog was then allowed to recover. The cervical vagi were exposed and bilateral thoracotomy and pericardectomy operations were done in six of these. In the other two dogs, the same experiments were carried out, but the thorax was not opened.

Observations

The effect of ECT on the rabbit's heart and ECG was difficult to interpret, even with direct visual observation, because the rapid rate and gross movement of the heart during ECT disturbed the cardiac electrodes and interfered with the action currents on the electrocardiogram. When ECT was applied to the head, very marked tachycardia (250+) was produced, with predominant ventricular arrhythmias. When the rabbit was shocked through the extremities, the heart went into ventricular fibrillation.

In the dogs under pentobarbital anaesthesia, ECT caused generalized muscle spasms with a brief convulsion. When the spinal cord was cut, ECT caused only gross muscle-twitching of the face. When the mid-brain was cut, only very slight extension of the paws was observed.

Cardiovascular Responses to Unmodified Shock

In the absence of drug-induced general anaesthesia or muscle relaxation with succinylcholine in the three preparations with spinal cord transection (C_2) and in the eight preparations with mid-brain transection, shocks applied at 100 to 140 volts for one to three seconds invariably caused cardiac asystole. This was observed visually in the chest, and on the arterial blood pressure tracings. The recordings of aortic blood pressure showed a sharp spike upward when the current was applied at the end of diastole followed by a precipitous fall. When the current was applied at the end of systole, the aortic blood pressure fell directly (Figs. 2 and 3). At the same time the venous pressure rose sharply to at least double the resting level.

During these experiments coloured fast-speed motion pictures were taken of the heart so that the effects of ECT during six shocks without premedication and during seven shocks after 1 mg. of atropine could be reviewed in slow motion. Whenever cardiac asystole occurred, first the auricles, and then the ventricles, were seen to distend, and the vascular markings as well as the myocardium became dark. The asystole was usually of brief duration (three to eight

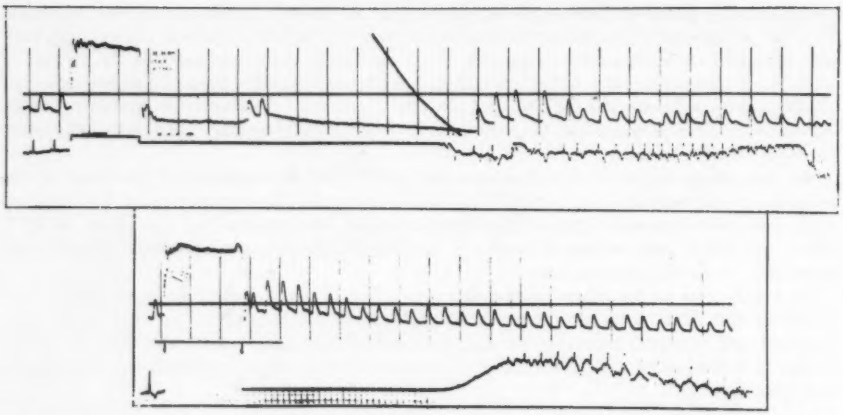

FIGURE 2. Aortic blood pressure and ECG (lead 2) tracings of a male dog, 27 lb. The mid-brain was previously transected under ether anaesthesia and the dog was allowed to recover. Bilateral thoracotomy and pericardectomy was performed. Respiration was controlled with compressed air.

Upper: No premedication; shock 120 v. for 2.2 sec.; observe immediate fall in aortic blood pressure after sharp rise which accompanied the flow of electric current (applied in diastole); asystole persisted for 11 sec. except for two beats.

Lower: Same dog 20 min. after intravenous administration of 0.5 mg. Antrenyl; shock 120 v. for 2.7 sec.; observe that heart continues to beat after the shock.

seconds) and varied with the strength and duration of the shock. The heart then began to beat again, very slowly at first, and then rapidly. Normal cardiac rate and rhythm returned spontaneously after several minutes. In one dog the asystole persisted for ninety seconds, at which time intermittent manual systole was applied. The heart responded after a few manual compressions, then gradually returned to a normal rate and rhythm.

In two dogs there was an abrupt onset of ventricular fibrillation after more than fifteen seconds of cardiac asystole (Fig. 4). In a third dog (mid-brain transection, thorax intact) the ECG and blood pressures did not alter significantly for twelve seconds after the shock, and again ventricular fibrillation began abruptly. Attempts to restore normal rhythm by manual systole and electrical defibrillation were unsuccessful in these animals.

In one dog after mid-brain transection electrodes were placed directly on the cortex through burr-holes. Cardiac asystole followed by tachycardia was observed with much lower currents than when the needle electrodes were placed in the scalp.

Stimulation of the vagus in the neck caused brief asystole when the current strength was sufficient (15–60 volts). Cutting both vagi in the neck, or cutting the left vagus and cooling the right vagus, invariably prevented cardiac asystole or other major cardiac disturbances (twenty-one experiments in six dogs).

The injection of 1 mg. of atropine (eight dogs, forty-eight experiments), 0.4 mg. of scopolamine (two dogs, eleven experiments), 0.5 mg. of oxyphenonium (one dog, nine experiments) or 1 mg. of hexocyclium (one dog, five experiments)

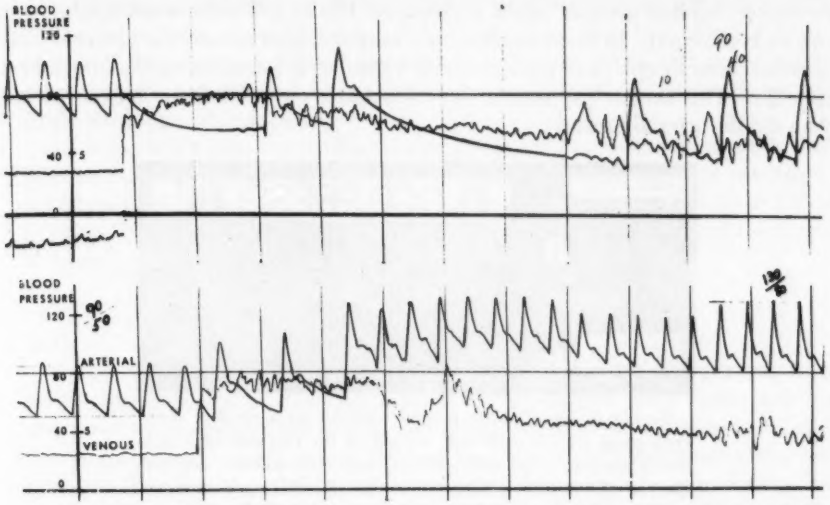

FIGURE 3. Aortic blood pressure, IVC pressure tracings of a male dog, weight 19 lb. The spinal cord was transected at C2 under ether anaesthesia, then the dog was allowed to recover. Bilateral thoracotomy and pericardectomy were performed. Respiration was controlled with oxygen.

Upper: No premedication; electroshock 120 v. for 1.0 sec.; observe the immediate fall in aortic blood pressure when current was applied early in diastole; asystole lasted 8 sec., except for two beats; then the arterial blood pressure returned to the resting level promptly; the venous pressure rose immediately from 3.5 mm. Hg to 10 mm. Hg and then gradually returned to the resting level during the succeeding 54 sec.

Lower: Same dog 15 min. after intravenous administration of 1 mg. atropine; observe the slight slowing of heart rate as the aortic blood pressure was rising, and then the slight acceleration in rate; the elevated blood pressure persisted for 140 sec.; venous pressure rose immediately as in the unpremedicated state, and returned to resting level slowly (120 v. for 1.0 sec.).

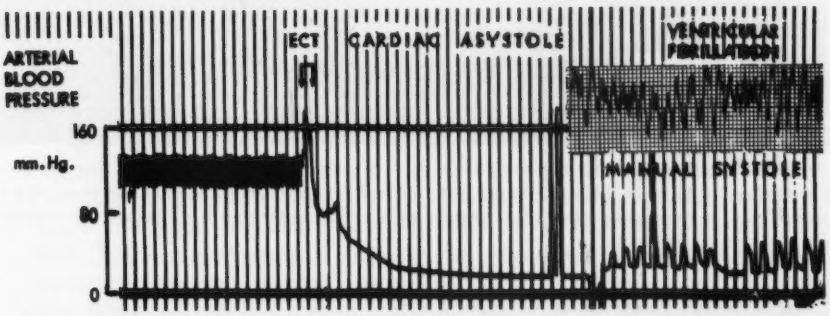

FIGURE 4. Aortic blood pressure of a male dog, 31 lb. The mid-brain was previously transected under ether anaesthesia and it was allowed to recover. Bilateral thoracotomy and pericardectomy were then performed, and respiration was controlled with compressed air. Electroshock, 120 v. for 1 sec. Observe sharp spike in aortic blood pressure when current applied at the end of systole, then the precipitous fall with absence of pulse waves for more than 20 sec. This was followed by two strong contractions and a fall to zero, at which time the heart went into ventricular fibrillation (ECG insert). Manual systole and attempts at electrical defibrillation were unsuccessful. This response occurred in two dogs.

prevented cardiac asystole when currents of 100 to 140 volts were applied for two to five seconds. In these experiments, both the arterial and the venous blood pressures rose sharply, and then gradually returned to normal after the convulsion subsided. The venous pressure always remained elevated for a longer period than did the arterial pressure.

FIGURE 5. Mean aortic pressure tracing on a smoked drum kymograph from a male dog, weight 44 lb. The mid-brain was previously transected under ether anaesthesia and the dog was allowed to recover. Bilateral thoracotomy and pericardectomy were then performed. Respiration was controlled with compressed air. No premedication was given. Electroshock, 140 v. for 3.8 sec. Observe marked fall in mean aortic blood pressure and almost complete absence of pulse wave oscillations for over 25 sec. followed by slow recovery.

FIGURE 6. Same dog as in Figure 5, 20 min. after premedication with 0.4 mg. scopolamine. Electroshock, 140 v. for 3.8 sec. Observe very marked rise in mean aortic blood pressure which took 40 sec. to return to resting level. Regular pulse wave oscillations were present throughout the hypertensive episode.

Cardiovascular Response to Modified Shock

The cardiovascular response to ECT appeared to be modified in the four dogs under pentobarbital anaesthesia, in that a greater voltage or duration of shock was required to arrest the heart or cause disturbance of cardiac rate and rhythm.

The intravenous injection of 20 to 45 mg. of succinylcholine one to two minutes preceding the application of electroshock eliminated the muscle twitching but

did not cause any significant alteration in the cardiac response, nor was there any alteration in circulatory dynamics, either before or after the administration of atropine. Dogs with mid-brain transection that were given 100 mg. thiopental intravenously immediately before shocking also showed no significant alteration in the cardiovascular response.

When a sufficiently strong electric shock was applied to the extremities or any part of the body (including the head) ventricular fibrillation was produced. It was then very difficult to restore normal rhythm. The voltage at which ventricular fibrillation occurred was very much higher when the current passed through the head only (> 120 volts, for at least two seconds).

Discussion

Under physiological conditions afferent impulses arising from nervous sinuses on the great vessels of the neck modify the respiration, heart rate, and blood pressure. Stimulation of the central end of the aortic nerve or the central end of the vagus nerve usually slows and weakens the heart and lowers the blood pressure. The slowing of the heart is probably due mainly to stimulation of the vagal nucleus, causing an increased discharge along the efferent vagal fibres, which are cardio-inhibitory. The fall in blood pressure following stimulation of these nerves may be due to decreased cardiac output and inhibition of vasomotor tone, leading to generalized vasodilatation and decreased peripheral resistance. Increasing the frequency of electrical stimulation applied to the central end of the vagus increases the rate of onset and degree of hypotension, and may delay recovery by causing brief cardiac asystole. Similar effects are produced by increasing the strength or duration of stimulation. Electrical stimulation of the sinus nerve produces similar results. Vagal section (bilateral) or injection of atropine eliminates this effect (2).

The same cardiovascular effects were observed when ECT was applied to the head of a dog in the manner used clinically for the treatment of mental disorders. These have also been reported when the cerebral cortex is stimulated directly (3, 4).

It has been postulated that vagal hyperactivity is responsible for the arrhythmias seen immediately *after* unmodified ECT. These arrhythmias were thought to be caused by reflexes activated when a large amount of blood was trapped in the periphery during the seizure and was then sucked into the great veins and right auricle as the seizure subsided. Altschule pointed out that this mechanism could not account for the early vagal activation seen immediately after ECT in the absence of a Grand Mal seizure response (5). However, our observations revealed a sharp rise in right auricular pressure (blood pressure in the inferior vena cava), corresponding in time with the tonic phase of the convulsion, so that the blood was evidently not trapped in the periphery, but seemed to be trapped or driven centrally on the venous side of the circulation. This effect was produced immediately by muscle contraction caused by the electric current and induced a sufficiently strong stimulation of the vagus to arrest the heart. Similar effects have been seen in man (6, 7). This certainly implicates

vagal hyperactivity as the main cause of cardiac asystole and subsequent cardiac arrhythmias.

Other possibilities have been suggested also. Direct stimulation of intracranial areas occurs, and may affect the cardiac rate through the vagus nerves (8). Stimulation of the hypothalamic centres may occur also during ECT and release posterior pituitary secretion into the spinal fluid causing cutaneous vasodilatation, lacrimation, salivation, and pilo-erection (9, 10, 11). However, it is unlikely that the latter is important in this situation because the clinical response is much too rapid to be explained by a reaction to a hormone secreted into the cerebral spinal fluid.

Another possibility has arisen since succinylcholine came into widespread use for modified ECT. It was shown in cats that although succinylcholine closely resembles acetylcholine, only the nicotinic actions and not the muscarinic actions of acetylcholine can be demonstrated on the circulation (12). It has also been demonstrated clinically that the single administration of 60 mg. of succinylcholine produces changes in circulatory dynamics in about 30 per cent of premedicated patients during induction of general anaesthesia. Initially a response similar to the muscarinic effect of acetylcholine was seen (bradycardia and hypotension), followed by a nicotinic response (tachycardia and hypertension). This effect could be blocked by atropine. Concurrently, changes in the ECG were observed, consisting of flattening of the T wave associated with a depression or "coving" of the ST segment. These changes in the ECG were unaffected by atropine (13).

It is possible that the above cardiovascular changes seen with succinylcholine were due to the hypoxia and hypercarbia associated with the muscle twitching that accompanies the depolarizing effect of the drug on skeletal muscle, together with the effect of the sudden arrest of breathing (14, 15, 16).

When smaller doses of succinylcholine were used (10–30 mg.) and the patient's lungs were well ventilated with oxygen, T-wave depression was observed only six times after 365 administrations of modified ECT (1). Alterations in the pulse rate and cardiac rhythm in these patients appeared to be related more to the convulsive reaction to ECT than to the thiopental and succinylcholine administered. Moreover, similar responses of the blood pressure, pulse rate, and ECG were observed during the presently reported experiments, even when succinylcholine was not given, and the cardiovascular response was not altered significantly when succinylcholine was added.

However, one should not rule out the possibility that in an occasional patient the administration of larger doses of succinylcholine (40–100 mg.) might potentiate the vagal stimulation produced by ECT. This effect must be guarded against also by adequate premedication with an anticholinergic drug and by ensuring adequate pulmonary ventilation until full spontaneous breathing returns.

Summary

The acute effects of electroconvulsive therapy have been reinvestigated on animals. Our experiments have shown that the effects of ECT on circulatory dynamics were due mainly to stimuli which reached the heart through the vagus

nerves. If these nerves were not blocked, electroshock with a current of duration employed clinically caused a brief period of asystole in almost every experiment, and occasionally caused death, either because of prolonged asystole, or by asystole followed by ventricular fibrillation. The previous administration of an anticholinergic drug in sufficient dosage to block the vagus nerves effectively eliminated the major cardiac reaction to electroshock. The intravenous injection of a moderate dose of thiopental did not appear to alter grossly the cardiovascular response, but did seem to reduce the physical reaction to the electric shock. A small dose of succinylcholine intravenously reduced the reaction of skeletal muscle to the electric shock but did not appear to affect the cardiovascular response to ECT.

Conclusions

Unmodified ECT usually causes cardiac arrhythmias, which are preceded by a brief period of cardiac asystole. This cardiac asystole frequently lasts long enough to cause cyanosis even with efficient pulmonary ventilation although no sequelae of a serious nature may be evident. Occasionally it may last long enough to cause cerebral or myocardial ischaemia (with myocardial infarction) which may result in a delayed death. In the rare case this cardiac asystole may persist until death.

As a result of the observations made in this study, one must assert that the indications for premedication with anticholinergic drugs far outweigh any objections to their use in patients requiring ECT. In the elderly patient with obvious cardiovascular disease, it is wise to administer at least 1 mg. of atropine intravenously a few minutes before treatment. In patients without evidence of circulatory disorders, the authors recommend the intramuscular administration of 2 mg. of atropine about thirty minutes before treatment.

Acknowledgments

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Résumé

Dans le but de préciser leurs effets sur la dynamique circulatoire, nous avons étudié, chez des animaux, la réponse spontanée aux traitements électroconvulsifs. Nous avons fait cette étude pour compléter notre observation clinique de malades mentaux soumis à des électrochocs, car il est difficile de recueillir des données précises et fiables au cours des convulsions. Cette étude s'imposait également pour nous aider à trouver les meilleurs moyens de diminuer les réactions cardio-

vasculaires sérieuses que l'on observe et pour prévenir les morts occasionnelles à la suite d'électrochocs.

Nous avons fait nos observations sur des lapins et des chiens soumis à des électrochocs avant et après des blocages des vagues par le froid, l'administration intraveineuse de pentothal et de succinylcholine et l'administration intraveineuse de médicaments anticholinergiques.

Pour chacun des animaux, nous avons contrôlé la respiration en employant un ventilateur à pression positive intermittente et un gros débit d'air et d'oxygène pour être assurés qu'il n'y aurait pas de réinspiration dans le système. Nous avons produit les chocs électriques en employant des électrodes ressemblant à des aiguilles placées dans le scalpe et un transformateur à pouvoir contrôlable. Nous avions exposé le cœur et les gros vaisseaux en pratiquant une thoracotomie bilatérale et une péricardectomie partielle. Les pressions sanguines étaient prises dans l'aorte et la veine cave inférieure en employant des cathéters rattachés à des manomètres; la lecture simultanée des pressions et de l'électrocardiogramme était rendue possible grâce à l'usage d'un oscilloscope à plusieurs canaux. Les tracés étaient enrégistrés par photographies. Pour quelques animaux, nous avons employé l'anesthésie générale et pour d'autres, nous avons sectionné la moelle ou le cerveau. Au cours des expériences, nous avons fait de la cinématographie rapide du cœur pour pouvoir ensuite, en ralenti, étudier ses réponses ou ses réactions.

Ces expériences ont démontré que les effets de l'électrochoc sur le cœur sont attribuables principalement à des influx nerveux atteignant le cœur par les vagues. Si l'on ne fait pas le blocage de ces nerfs, l'électrochoc, avec les courants de force et de durée employés en clinique, produit, dans presque tous les cas, une brève période d'asystolie. A l'occasion, il peut survenir une mort par asystolie prolongée ou l'installation soudaine d'une fibrillation ventriculaire à la suite d'une brève asystolie. Les médicaments anticholinergiques éliminent efficacement la principale réaction cardiaque à l'électrochoc.

A la suite de ces études, nous en venons à la conclusion qu'il est dangereux, particulièrement chez les vieillards, de donner des électrochocs sans atténuation. L'asystolie cardiaque que produisent ces traitements peut souvent durer assez longtemps pour entraîner de la cyanose, même si la ventilation pulmonaire est adéquate. Habituellement des séquelles sérieuses peuvent passer inaperçues. Mais, à l'occasion, l'asystolie peut être assez prolongée pour produire une ischémie cérébrale ou myocardique et entraîner ultérieurement la mort. Plus rarement, l'asystolie persiste et c'est la mort immédiate. En conséquence, nous conseillons d'administrer de l'atropine, par voie intramusculaire, avant tout électrochoc; chez les vieillards, à la dose de 1 mg. et chez les plus jeunes, à la dose de 2 mg.

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SEROTONIN AND THE CARCINOID SYNDROME

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WHEN BLOOD clots, a vasoconstrictor substance is released from the disintegrating platelets. The isolation of this principle from beef serum was described in 1948 by Rapport, Green and Page (1) who later identified it as 5-hydroxytryptamine. For this vasoconstrictor principle, Corcoran coined the word serotonin. Many years previously Erspamer studied a vasoconstrictor substance associated with the enterochromaffin system of the gastro-intestinal tract which he called enteramine. This he later identified as identical with 5-hydroxytryptamine or serotonin.

The presence of large amounts of serotonin in carcinoid tumours, the description by Biörck (2) of a bizarre syndrome associated with metastatic malignant carcinoid and attributable to excessive serotonin production, and the discovery of this substance in the brain (3) stimulated much research to elucidate the functions of the amine in health and disease.

Although the precise functions of serotonin are still obscure there can be little doubt that it is a substance of great physiological importance. The anaesthesiologist in his role as the applied physiologist of the surgical team should be aware of how this compound, especially when present in excessive amounts as in the carcinoid syndrome, can effect the homeostasis of his patient and modify the actions of the agents he uses to produce anaesthesia. In this paper some of the actions of serotonin will be described, with particular reference to the carcinoid syndrome, and an attempt made to indicate how these may modify the choice and conduct of anaesthesia in patients suffering from that condition.

SOURCE, SYNTHESIS, AND DISTRIBUTION (4, 5)

Serotonin is widely distributed in the body. Large amounts are found in the brain, blood platelets, and gastro-intestinal tract. Smaller quantities are present in the liver and bone marrow while little occurs in the lungs, thyroid, pancreas, and diaphragm. None is present in skeletal muscle, the peripheral nerves, or the adrenal glands.

The dietary precursor of serotonin is the amino-acid tryptophan. This becomes hydroxylated, probably in the liver, to 5-hydroxytryptophan (5-H-T-P) which then undergoes decarboxylation to form 5-hydroxytryptamine or serotonin. The specific decarboxylase for 5-H-T-P is found in most tissues, particularly in the brain, lungs, liver, kidneys, and sympathetic ganglia. Serotonin is mainly broken down and excreted in the urine as 5-hydroxyindole acetic acid (5-H-I-A-A), the enzyme responsible being the widely distributed monamine oxidase. The quantitative excretion of 5-H-I-A-A may, therefore, be used as an index of serotonin metabolism.

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Functions of Serotonin in the Maintenance of Homeostasis

Serotonin-buffering System

In experiments to determine the effect of injections of serotonin on the cardiovascular system conflicting results were often obtained. For example, in a given series of patients, following injection of the amine, the blood pressure may be raised, lowered, or undergo a biphasic response. In order to try and explain these findings the concept of a serotonin-buffering system was advanced (6). This ascribes to serotonin the role of humoral antagonist to neurogenic vasomotor tone, the vascular response to the amine being largely determined by the degree of tone present. When this is high, the response is hypotensive and when low a pressor effect is seen. There is probably both a central and a peripheral inhibitory effect of the hormone on neurogenic tone.

Blood

Nearly all the serotonin of the blood is found in the platelets and is released when these disintegrate. When applied directly to blood vessels, serotonin exerts a vasoconstrictor effect and it is tempting to ascribe to it some role in the haemostatic mechanisms. This assumption is not confirmed experimentally, however. It is possible in man by administration of reserpine to cause marked and prolonged depletion of the serotonin content of the platelets, brain, and gastro-intestinal tract without influencing the clotting mechanism or haemostasis (7). However, some workers have suggested that serotonin might be an antagonist of antithrombin, thus facilitating the conversion of fibrinogen to fibrin (8).

The observations that the platelets in the carcinoid syndrome contain excessive amounts of serotonin, and that ordinary platelets are capable of absorbing large amounts of this amine, indicate the possibility that platelets may be concerned in the fixation and inactivation of this potent humoral agent by binding to the platelet constituents in an inactive form (4). Conversely, of course, it can be argued that when stored in platelets serotonin is protected from destruction by amine-oxidase, to be available for release when required.

Gastro-intestinal Tract

A large proportion of the body serotonin occurs in the gastro-intestinal tract where it is formed by the enterochromaffin cells. Its physiological function in the alimentary canal is unknown, but it probably serves as a local hormone to regulate smooth muscle function. The increased intestinal motility produced by injection of serotonin and the diarrhoea and colic characteristic of the carcinoid syndrome tend to support this theory.

The Brain (4, 5)

The brain contains relatively large amounts of serotonin, the greatest quantities being located in the hypothalamus and other areas concerned with autonomic activity. Parenterally administered serotonin does not readily cross the blood-brain barrier, the brain probably synthesizing its own serotonin from 5-H-T-P and metabolizing it with monamine oxidase.

Interest was aroused concerning the possible functions of serotonin in the

brain by the discovery that administration of the tranquillizer reserpine caused release of serotonin from the body depots with a marked increase in the excretion of 5-H-I-A-A. The brain serotonin is especially susceptible to reserpine release and naturally some connection between the ataractic effect of this drug and its ability to release serotonin was postulated. However, the distribution of norepinephrine in the brain closely parallels that of serotonin and reserpine reduces its concentration at about the same rate. This tranquillizer also stimulates release of catechol amines from the innervated adrenal medulla and norepinephrine from the cervical sympathetic ganglia. Thus reserpine brings about changes in the distribution of three very active amines so that a simple explanation for its tranquillizing action is unlikely.

The precise functions of serotonin in the central nervous system remain obscure though many theories have been advanced. Brodie and Shore (30) suggest that it may be the transmitter substance for stimulation of subcortical parasympathetic centres or inhibition of sympathetic centres. Marrazzi and Hart (31) report that the hormone is a potent inhibitor of central sympatic transmission while Dobkin (9) suggests that optimum nerve function depends on the ratio of intracellular to extracellular serotonin. With a relative increase in intracellular serotonin there is increased tension, alertness, irritability, and a tendency towards convulsive behaviour. Conversely, an excess of extracellular serotonin results in depression and withdrawal.

Respiratory System

Serotonin is a potent bronchoconstrictor. Herxheimer (10) has reported that inhalation of serotonin aerosol in four normal subjects had no effect, while in three of six people with asthma severe asthmatic attacks were precipitated, which responded to isopropylnoradrenalin. In retrospect, he believes this effect was due to the acidity of the aerosol solution used. When a buffered, neutral solution was used no attacks were seen. However, inhalation of serotonin aerosol in guinea pigs produced a shock-like syndrome with dyspnoea, cyanosis, and often convulsions. Some relief was obtained with atropine. It is noteworthy that "asthmatic" attacks are characteristic of the carcinoid syndrome and are probably induced by release of serotonin from the tumour.

A constant decrease in tidal air occurs following injection of serotonin intravenously (11). This reduction is probably by bronchoconstriction, the effect being partly antagonized by atropine.

When injected, serotonin produces a rise in venous, right atrial, and pulmonary artery pressures with a fall in systemic blood pressure (12). The mechanism is probably by pulmonary vasoconstriction. These findings have led Smith and Smith (13) to implicate serotonin release from blood clot and infarcted lung as a factor in the production of the systemic effects of pulmonary embolism.

Potentiation of Choline Compounds and Inhibition of Cholinesterase

Fried and Antopol (14) found that very low concentrations of serotonin augmented the effect of human pseudo-cholinesterase, while higher concentrations caused marked inhibition. They comment that the potentiating effect at low

concentrations may be of greater significance than inhibition at higher concentrations as these low levels probably more nearly correspond to physiological values for the amine. This raises the possibility of cholinesterase inhibition by serotonin in conditions where its circulating level is above physiological limits, as in the carcinoid syndrome.

The work of Pick (15) showed that pre-treatment with small doses of serotonin strongly potentiated the effect of acetylcholine on the guinea-pig ileum. Serotonin also enhanced, but to a lesser extent, the effect of the more stable choline compounds. He does not believe that this potentiation can be explained solely on the basis of simple cholinesterase inhibition.

These findings are of significance to the anaesthesiologist concerned with the use of muscle relaxants. Consider neuromuscular blockade produced by a non-depolarizing relaxant such as tubo-curare. Serotonin would be expected to potentiate the effect of acetylcholine at the motor end-plate leading to its accumulation in this region. This would result in displacement of the curare from the cholinergic receptors of the end-plate and a reversal of the blockade. This hypothesis receives some support from the work of Philippot and Dallemagne (16). These workers found that in cats partial neuromuscular blockade produced by tubo-curare was rapidly reversed by injection of serotonin. No effect was seen in blockade produced by the depolarizing relaxant decamethonium iodide. With more intense blockade by curare, repeated injections of serotonin were necessary to produce reversal.

This reversal of neuromuscular blockade was independent of any variations in arterial pressure produced by the injection of serotonin. They do not believe that release of adrenalin following the injection of serotonin is a factor in producing reversal as this occurs too rapidly for any but a direct action and is also seen when injection of the hormone produces a fall in systemic blood pressure.

Since the introduction of succinylcholine as a depolarizing muscle relaxant, many cases of prolonged apnoea following its use have been reported. Though this apnoea can be caused by many mechanisms (17), the following may be relevant to this discussion.

Restoration of neuromuscular conduction following succinylcholine block is due to enzymatic hydrolysis, by plasma cholinesterase, of the succinylcholine to succinylmonocholine and then to succinic acid and choline. If cholinesterase activity is inhibited by serotonin, the rate of breakdown will be decreased, and the duration of blockade prolonged. With the slowing of the rate of breakdown of the relaxant, accumulation of the primary breakdown product succinylmonocholine will also occur. This compound has some neuromuscular blocking action, being about a twentieth as active as succinylcholine.

Thus, in conditions associated with an increased level of circulating serotonin, it may be postulated that the use of depolarizing muscle relaxants, especially succinylcholine, carries a risk of prolonged neuromuscular blockade due to cholinesterase inhibition.

Prolongation of Hypnosis by Serotonin

Correll and co-workers (18) noted that rats rendered unconscious with a variety of barbiturates often succumbed to minute quantities (often as little as

0.1 mg.) of serotonin given intravenously. Unanaesthetized animals tolerated up to 50 mg./kg. Similar results were obtained with light ether anaesthesia, 0.1 mg. of serotonin given intravenously killing four out of ten rats. It is interesting to note that with light cyclopropane anaesthesia, 0.1 mg. intravenously did not kill any of the rats, 0.5 mg. being necessary to kill five out of ten. They conclude that the intravenous injection of serotonin into an anaesthetized animal enhances the respiratory depression produced by the anaesthetic agent so that death appears to be the result of respiratory failure.

In view of the greater sensitivity to serotonin under light ether anaesthesia, which stimulates respiration, than under cyclopropane, which is a marked respiratory depressant, this explanation seems unlikely.

Brodie (19) showed that reserpine markedly potentiates the hypnotic effects of hexobarbitone and ethyl alcohol in mice, probably by causing release of serotonin. Reserpine does not increase the rate of bio-transformation or affect the rate of uptake by the brain of the two hypnotics. It presumably acts by increasing the sensitivity of the nervous system to these agents.

The same workers found that the sleeping times of mice under hexobarbitone (20) and pre-treated with serotonin were some 300 per cent longer than in mice given the barbiturate alone. This effect was substantially diminished by the prior administration of a serotonin antagonist (L.S.D.).

In confirming the hypnosis-prolonging properties of serotonin in mice anaesthetized with cyclobarbitone and chloral hydrate, Fastier (21) suggests that the ability of this hormone to prolong narcosis may be due to a relatively unspecific vascular effect, rather than to a more specific action on the nervous system. As he points out, this potentiating action of serotonin extends to several different kinds of hypnotics—barbiturates, alcohol, and chloral hydrate—which are metabolized in different ways. Thus, any explanation of its action on the basis of the inhibition of a specific enzyme system in the brain is unlikely.

Later work by Fastier (22) revealed that the potentiation of hypnosis by serotonin in mice anaesthetized with chloral hydrate was related to the hypothermic action of this hormone. This is enhanced in the presence of the hypnotic. The sleep-prolonging effect is much reduced when the environmental temperature is raised to make heat loss minimal. This hypothermic effect may be mediated centrally via the hypothalamus or peripherally by a direct action on the blood vessels.

Other workers (23) have shown that the injection of very small amounts of serotonin intravenously will exert a marked inhibitory effect on the brain-wave rhythms as seen under thiopentone anaesthesia. Paradoxically, under ether anaesthesia or unanaesthetized, the effect is excitatory, tending to increase the frequencies of these waves.

That these observations find clinical application will be shown in the discussion on anaesthesia in the carcinoid syndrome. Purely in the realms of conjecture, it is fascinating to speculate as to the possible part serotonin may play in the prolonged unconsciousness seen after some head injuries; the excessive somnolence associated with certain hypothalamic disorders and the narcoleptic state. Of more direct interest to the anaesthesiologist, what is its role, if any, in the phenomenon

of artificial hibernation? Is its metabolism altered in those patients who show abnormal sensitivity to the barbiturates? The field is indeed fascinating and the possibilities seem legion.

The Pituitary-Adrenal System

Moussatche and Pereira (24) have shown that the administration of serotonin to rats decreases the ascorbic acid content of the adrenal glands. This did not occur in hypophysectomized animals, indicating that the mechanism is through release of A.C.T.H. This action is blocked by the serotonin antagonist B.O.L. Others (25) have demonstrated an increase in platelets and decrease in eosinophils following injection of a large dose of serotonin in rats. Munson (26) has shown that reserpine can stimulate the secretion of A.C.T.H. and, after administration of this drug, other stressful agents no longer have their usual effect on A.C.T.H. production. These findings have stimulated interest in the possibility that serotonin may be the hypothalamic neuro-humor responsible for stimulating A.C.T.H. secretion.

In patients with the carcinoid syndrome there is an increased incidence of adrenocortical hyperplasia and adenomas (27), indicating possible persistent stimulation by A.C.T.H. They are also more susceptible to overwhelming bacterial infections which may be anticipated if long-continued adrenal stimulation has resulted in their inability to respond to additional stress by increased output of steroids.

Apparently, then, these patients might be expected to have a poor adrenal response to the stress of anaesthesia and surgery so that supplemental steroid therapy may become necessary.

Additional Functions

Evidence is accumulating that serotonin may be concerned in many other vital functions. This has been reviewed by Page (5) and will only be briefly mentioned. The hormone may be involved in the vascular changes and pain produced in the early phases of inflammation. The amine is released in anaphylactic shock and certain antigen-antibody reactions; it may also be concerned in the regulation of sodium metabolism.

These actions of serotonin may be related to its ability to produce a selective alteration in the permeability of the cell membrane.

Intestinal Carcinoid and the Malignant Carcinoid Syndrome

Carcinoid tumours arise in the enterochromaffin cells and comprise (5, 27, 28) about 1 per cent of all neoplasms of the gastro-intestinal tract. They can occur anywhere from the stomach to the rectum, but are usually found in the ileo-caecal region. In about 25 per cent of these neoplasms, especially those associated with hepatic metastases, a peculiar syndrome occurs, characterized by all or some of the following features: (1) colicky abdominal pain, borborygmi, hypermotility of the bowel, and watery diarrhoea; (2) a violaceous cyanosis, intermittent flushing of the skin associated with tachycardia and telangiectasia; (3) right-sided endo-

cardial fibrosis with pulmonic stenosis and tricuspid regurgitation leading to right-sided heart failure with hepatic congestion and dependent oedema; (4) "asthmatic" attacks associated with cyanosis, flushing, and dyspnoea.

Tumour extracts and the blood of patients with this syndrome contain large amounts of serotonin, while the excretion of 5-H-I-A-A is greatly increased. Many of the features of the syndrome can be reproduced by the administration of exogenous serotonin and it seems reasonable to assume that carcinoids are endocrine tumours producing excessive amounts of the hormone serotonin. About two-thirds of the free circulating serotonin is removed during passage through the lungs.

The flushes of the syndrome are related to falls in blood pressure and are probably mediated through release of serotonin from the tumour and metastases. Sudden release of serotonin into the circulation may occur with handling of the tumour or be precipitated by a fall in blood pressure.

The serotonin antagonists are peculiarly ineffective in controlling the symptoms of the syndrome, though some symptomatic relief is usually obtained with chlorpromazine.

With physicians becoming increasingly aware of the existence of the syndrome, improved methods of diagnosis, the relatively slow growth and spread of the tumour, and its frequent association with other surgical conditions, the anaesthesiologist will no doubt be more frequently called upon to anaesthetize patients with this condition in the future. Anaesthesia may be required for an exploratory laparotomy, attempted excision of the tumour and metastases, or relief of intestinal obstruction produced by the growth. Also surgical treatment of an associated cholecystitis, cholelithiasis, or peptic ulceration, which show an increased incidence in association with this disease, may become necessary.

In deciding which methods and drugs to use in the anaesthetic management of patients with these conditions, there are several factors the anaesthesiologist must consider.

Many of the patients have been taking chlorpromazine over a prolonged period for symptomatic relief of some of the manifestations of the syndrome. This tranquillizer produces peripheral vasodilation, mild hypotension, and tachycardia. There is a well-marked adrenolytic action and orthostatic hypotension readily occurs. The drug also potentiates the effects of hypnotics, narcotics, and relaxants so that prolonged apnoea and delayed return of consciousness may complicate the picture.

The avoidance of hypotensive episodes is especially important in these patients as there is evidence that falls in blood pressure can release serotonin into the circulation from the tumour and metastases (29). If hypotension occurs, its reversal by vasopressors may be difficult as the response to these drugs is modified by chlorpromazine. Phenylephrine and L-noradrenalin are the vasopressors of choice, the less potent agents such as ephedrine, methyl amphetamine, and methoxamine being singularly ineffective in the presence of the tranquillizers.

The development, during the course of operation or postoperatively, of a prolonged hypotension refractory to powerful vasopressors and not associated with blood loss is likely to indicate adrenocortical insufficiency. This may be due to

exhaustion of the adrenal cortex following prolonged stimulation by A.C.T.H. released by serotonin. In this state patients react poorly to the stress of anaesthesia and surgery so that hypotension, respiratory depression, and delayed recovery are seen.

Treatment of this complication is by intravenous steroids although if its existence is suspected preoperatively the use of steroids before and after operation may prevent its occurrence.

Small amounts of narcotics and sedatives should be used in the premedication of these patients as marked potentiation of the effects of these agents occurs with both chlorpromazine and serotonin. Atropine should be given in full dosage, in view of the experimental work indicating a protective effect against serotonin-induced bronchoconstriction.

Endotracheal intubation is mandatory to ensure perfect oxygenation at all times, especially if the cardiac lesions sometimes associated with the syndrome are present. Intubation also ensures easy access to the tracheobronchial tree so that rapid and efficient treatment of any "asthmatic" attack is possible.

Induction and maintenance with cyclopropane are recommended in light of the finding that rats anaesthetized with this gas are more resistant to the lethal effects of injected serotonin. Also with this agent, high oxygen concentrations can be given and excellent muscular relaxation obtained, if required, with only small amounts of relaxant. The slight increase in blood pressure often seen in light cyclopropane anaesthesia is also of benefit in avoiding hypotensive episodes.

The use of barbiturates is contra-indicated because of the potentiation of hypnosis produced by both chlorpromazine and serotonin. Another disadvantage is the frequent occurrence of hypotension during induction. This fall in blood pressure is exaggerated in the presence of chlorpromazine.

If the use of a muscle relaxant becomes necessary, curare is the agent of choice owing to the risk of the prolongation of muscle blockade following the use of depolarizing relaxants.

During the course of the surgical procedure, sudden release of serotonin from the tumour may occur following a period of hypotension or handling of the neoplasm. The increase in circulating serotonin may precipitate an "asthmatic" attack with bronchoconstriction and cyanosis. Treatment is by intravenous atropine, and phenylephrine by nebulization into the anaesthetic circuit.

In the postoperative period, careful watch must be kept to detect any hypotension, shock, and respiratory depression. These may develop suddenly and prove resistant to treatment for reasons already discussed.

Summary

A brief description of some of the main physiological actions of serotonin has been given. Their clinical implications, especially where they pertain to the field of anaesthesia, are presented in some detail.

The malignant carcinoid syndrome is discussed and some of the problems which may confront the anaesthesiologist in dealing with patients suffering from this condition are mentioned.

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RÉSUMÉ

La sérotonine (5-hydroxytryptamine) est une hormone que l'on trouve en grande quantité dans le cerveau, les plaquettes sanguines et le tractus gastro-intestinal. L'on ne connait pas précisement son rôle dans le maintien de l'homéostase, mais des travaux de laboratoire nous font croire qu'elle joue un rôle dans le maintien de plusieurs fonctions vitales de l'organisme.

En se désagrégeant, les plaquettes sanguines libèrent cette hormone en grande quantité; on ne peut pas affirmer que ce fait influence les mécanismes de l'homéostase. Dans le tractus intestinal, la sérotonine est sécrétée par les cellules entérochomaffines. Il est possible que cette sécrétion locale serve à la régulation de la contraction des muscles lisses.

La découverte que la réserpine provoque une libération de sérotonine dans le cerveau n'a pas manqué de soulever de la curiosité sur son rôle dans le fonctionnement du système nerveux central. C'est un inhibiteur de la transmission synaptique centrale et il est possible que ce soit un véhicule chimique des stimuli destinés aux centres parasympathiques sous-corticaux.

Sur l'arbre respiratoire, cette hormone produit de l'hypertension et de la bronchoconstriction.

En laboratoire, on a établi que la sérotonine inhibait la pseudo-cholinestérase humaine. En conséquence, dans les états où il y aurait une augmentation de la sérotonine circulante, il y aurait un risque additionnel, à cause de l'inhibition de la cholinestérase, à employer des agents curarisants du type dépolarisant de crainte d'avoir à faire face à un blocage neuromusculaire prolongé.

La sérotonine potentialise l'action de plusieurs hypnotiques, des barbituriques, de l'alcool et de l'hydrate de chloral. Cet effet dépend de l'action hypothermisante de la sérotonine, effet qui peut être considérablement diminué par l'administration de L.S.D., un antagoniste de la sérotonine.

L'administration de sérotonine provoque une libération d'A.C.T.H. cela ne manque pas d'intérêt si l'on songe à la fréquence accrue des hyperplasies adrénocorticales et des adénomes chez les malades présentant un syndrôme carcinoïde.

Le syndrôme carcinoïde est causé par la libération de grandes quantités de sérotonine venant de tumeurs carcinoïdes des cellules entérochromaffines, plus particulièrement quand il existe des métastases hépatiques. Ce qui le caractérise, c'est une douleur abdominale ressemblant à une colique, de la diarrhée, des attaques d'asthme et de la fibrose du cœur droit. Des manipulations de la tumeur ou une chute de tension artérielle peuvent provoquer une libération de sérotonine.

On a souvent besoin d'administrer une anesthésie à ces malades et il s'impose, pour l'anesthésiste, d'apporter une attention spéciale. Un grand nombre de ces malades prennent de la chlorpromazine pour soulager leurs coliques et leur

diarrhée. Comme prémédication, on peut prescrire de petites quantités de narcotiques et de sédatifs, mais il faut avoir recours à l'atropine à hautes doses. Nous conseillons une induction et un maintien de l'anesthésie au cyclopropane et déconseillons l'usage des barbituriques. Le myorésolutif de choix demeure le curare puisque les dépolarisants sont contrindiqués. Il faut éviter l'hypotension car elle peut entraîner la libération de sérotonine. S'il faut avoir recours à des vasopresseurs, il faudrait employer de la phenylephrine et de la L-noradrénaline car il peut arriver que, avec des agents moins puissants, on éprouve de la difficulté à corriger l'hypotension à cause des effets adrénolytiques de la chlorpromazine.

Si, en l'absence d'hémorragie, on est en face d'une hypotension marquée et prolongée, il faut songer à une insuffisance adrénocorticale et recourir à l'usage des stéroïdes. On peut observer, au cours de l'anesthésie, des crises asthmatiformes avec bronchoconstriction et cyanose. Il faut administrer de l'atropine par voie endoveineuse et nébuliser dans le circuit de la machine à anesthésie de la phenylephrine. Dans les suites opératoires, il faut exercer une surveillance de tous les instants car, soudainement, il peut survenir une hypotension, un état de choc et une dépression respiratoire.

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INTRAMUSCULAR SUCCINYLCHOLINE FOR ENDOTRACHEAL INTUBATION IN INFANTS AND CHILDREN[1]

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THE INDUCTION and intubation of an adult are seldom a problem, whereas the intubation of an infant or a child may be difficult, owing to the fact that, if not heavily premedicated, he may fight against the inhalation agent imposed upon him and make intravenous injection impossible, especially if the anaesthetist is working alone.

In a busy hospital, it is not so simple to postpone a relatively minor operation, such as tonsillectomy, hernia, or squint, solely because the child is not well premedicated, and is excited and crying. In such cases wrestling with the child usually results, especially if one tries to impose upon it the Vinethene-ether sequence which is still so popular in our hospitals or the more violent force of intubating a conscious baby with topical anaesthesia.

We have tried to simplify and shorten the induction period for intubation in the infant and child, and to make it easier for the anaesthetist and safer for the bad risk patient, by giving succinylcholine intramuscularly prior to the intubation.

In all cases succinylcholine was used in the form of Anectine (Burroughs Wellcome & Co.). The Anectine was always taken fresh from the refrigerator.

One hundred and fifty-five patients between three days and fourteen years of age have been intubated by this method. Operations performed were:

ENT, mainly tonsillectomies	63	Cardiac surgery	7
Hernias	21	Neurosurgery	6
Eye operations	13	Intra-abdominal	4
Circumcisions	11	Dental surgery	3
Plastic surgery	10	Others	8
Accidental injuries	9		

The action of the intramuscular Anectine was considered satisfactory if the patient was fully relaxed by the time of intubation done within three minutes after the injection of the relaxant. Fully relaxed here means a complete flaccid paralysis of all striated muscles including the laryngeal muscles (the same as if the drug had been given intravenously).

Four variations of induction were used.

In the first, oxygen only was given before and after the injection and intubation in two cases of imminent death due to respiratory insufficiency resulting from severe convulsions. Patients dramatically improved.

In forty cases Anectine was given intramuscularly to the conscious patient, immediately followed by nitrous oxide–oxygen 6:3 by mask. The mask was lowered gradually to the patient's face, and the respiration assisted as it became shallow, and then controlled for a minute when it had ceased; then intubation

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was performed. Controlled respiration with N_2O–O_2 was continued after the intubation until the patient's spontaneous respirations started (that is, when slight spontaneous movements of the diaphragm were noticed). From this point on, ether, trilene, Fluothane, or cyclopropane was added and gradually increased, and the respiration was assisted until clinically sufficient respiration was present—that is, when the tidal volume seemed to be satisfactory, and there were no signs of anoxia.

When Anectine was used in conscious patients, the following observations were made.

If the patient was crying prior to the injection, he lost his voice in 30 to 45 seconds after the injection, although the muscles of the extremities still seemed to be very strong, and the patient was able to lift his head for approximately ten seconds more. Most of the patients became co-operative by the time they had lost their voices, as they were now able to listen to the voice of the anaesthetist, and started breathing as deeply as possible the anaesthetic mixture of N_2O or cyclopropane, which was flown over their faces. When the patient was restless, and did not want to lie down, the injection was done with the child still in the nurse's arms, or sitting on the operating table. When the head of the patient became too heavy, 45 seconds after the injection, he was placed horizontally, and gradually assisted, and then controlled respiration was started with the above mixture which seemed to render the patient unconscious within a minute.

Although I do not think that this was the right way to apply this method, it still seems to be gentle in comparison with the Vinethene-ether sequence in the resisting patient or conscious intubation with topical anaesthesia. Once the relaxant was given no force at all had to be applied by the anaesthetist.

In order to record the sensations of the patients a few older and co-operative children (one of 14 years) were induced by giving Anectine intramuscularly in the conscious state. The following is an example.

A very co-operative 10-year-old boy, weight 60 lb., underwent tonsillectomy. He was given 1.2 c.c. of 10 per cent Anectine intramuscularly. After ten seconds the patient said that it did not hurt any more and it was less painful than the injection of the premedication (Demerol, Atropine), which was easily explained as the premedication was given subcutaneously. Then 20 seconds after the injection the patient said: "I feel that I am getting very tired and heavy." His voice was lost 30 seconds after the injection. His respiration became shallow 45 seconds after the injection, although the patient was still able to move his right hand if asked to do so. Assisted respiration with N_2O–O_2 was started right away, and controlled respiration one and a half minutes after the injection, when there was a complete flaccid paralysis, and apnoea. Intubation was performed three minutes after the injection with very good relaxation. Slight diaphragmatic movements appeared six minutes after the injection, which was considered as the commencement of spontaneous respiration. Trilene was added to the N_2O–O_2 mixture, and gradually increased. Recovery of the respiration, to the point where assisted respiration was considered no longer necessary, followed within the next nine minutes (that is, respiration was satisfactory 15 minutes after the intramuscular injection of Anectine). The operation was finished, and the patient was extubated, and was breathing well 23 minutes after the injection.

The third variation of the induction was used in ninety-nine patients—that is, in most of them. Here a concentrated mixture of cyclopropane–O_2 or N_2O–O_2 was

allowed to flow over the face of the patient as the mask was gradually lowered. As soon as the patient was unconscious, usually two minutes after commencing the induction, Anectine was given intramuscularly, and N_2O–O_2 alone was given in all cases, with assisted and controlled respiration prior to intubation, so that relaxation at the time of intubation was entirely due to the Anectine injected.

The fourth variation was used for bad risk patients, and in cardiac surgery in fourteen patients. The patients, of course, were well premedicated and calm or sleeping if not roused. Cyclopropane–O_2 was given by mask until the patient was unconscious; then Anectine was given intramuscularly and assisted and controlled respiration performed as necessary. The vocal cords and trachea were sprayed with 4 per cent Xylocaine prior to the intubation. Cyclopropane–O_2 was continued after the intubation until intravenous infusions were installed or a venous cut-down performed. During this type of induction, we did not notice any change in blood pressure and only a slight slowing of the pulse rate if the concentration of cyclopropane was increased. After the installation of intravenous infusions, intravenous Anectine drip was started, and the patient was maintained on N_2O–O_2 anaesthesia during the operation.

Amount and Concentration of Anectine

Anectine 2 per cent or 20 mg./c.c.

Dosage: *1 mg. per pound of body weight.* This dosage was used in nineteen patients, aged two weeks to six years. Nine of these were not completely relaxed within three minutes. Although seven of them could be intubated with more or less difficulty, two were not sufficiently relaxed for intubation (that is, the results were not fully satisfactory in 50 per cent of the patients).

Dosage: *1¼ mg. per pound of body weight.* This dosage in thirty patients, aged two months to seven years resulted in 33 per cent of the patients being incompletely relaxed within three minutes after the injection, although it was possible to intubate all of them without an additional dose of relaxant.

Dosage: *1½ mg. per pound of body weight.* In twenty-seven patients, aged eight months to seven years, this dosage resulted in 30 per cent of the patients being incompletely relaxed, although intubation was possible in all cases.

Dosage: *2 mg. per pound of body weight.* In twelve patients, aged three days to three years, this dosage resulted in complete flaccid paralysis in all patients within two minutes of the injection of the Anectine.

Anectine 10 per cent or 100 mg. per c.c.

Dosage: *1½ mg. per pound of body weight* was given intramuscularly in thirty-nine patients, aged eight months to fourteen years. Six patients, that is 17 per cent, were not fully relaxed and did not stop breathing completely although intubation was possible in all of them.

Dosage: *2 mg. per pound of body weight* were given in twenty-eight patients, eight months to thirteen years old. All of these were fully relaxed, and intubated, within three minutes of the injection.

Table I shows the amount of Anectine in milligrams per pound of body weight given in numbers of patients, in different age groups. In brackets the number of patients not fully relaxed at the time of intubation, that is, three minutes after the injection of Anectine.

TABLE I

Age	1 mg.	1¼ mg.	1½ mg. (2%)	1½ mg. (10%)	2 mg. (2%)	2 mg. (10%)	Total no. of patents
Under 1 yr.	6 (1)	3 (1)	4	2	8	2	27
1 yr.	2 (2)	5	3 (1)	3	1		17
2 yrs.	1 (1)	1 (2)	4 (2)	4	2	2	20
3 yrs.	1 (1)	5	3 (2)	11	1	7	31
4 yrs.	(1)	4 (2)	1	3 (1)		4	16
5 yrs.	(2)	1 (3)		5 (1)		5	17
6 yrs.	(1)	1 (1)	2 (3)	4 (1)		3	16
7 yrs.		(1)	1	1		2	5
8 and 9 yrs.				(2)		1	3
10 yrs.						1	1
13 and 14 yrs.				(1)		1	2
TOTAL	10 (9)	20 (10)	19 (8)	33 (6)	12	28	155

Table I indicates that smaller or younger children need less Anectine intramuscularly. They seem to have much faster absorption, and the level of succinylcholine in blood necessary for skeletal muscular paralysis is attained with smaller dosages.

If the concentrated Anectine (100 mg./c.c.) was used, the relaxation was attained in a shorter period of time, as the absorption of the same amount of water carries more Anectine with it. It also seemed to be less painful if in a child of 50 lb. 1 c.c. of the concentrated Anectine was injected, instead of 5 c.c. of the 2 per cent solution.

The following minimal dosages were found necessary in order to attain full relaxation in all patients in the following age groups: younger than twelve months—1½ mg./lb. of body weight of 2 per cent Anectine; one to three years—1¼ mg./lb. of body weight of 10 per cent Anectine; four years and older—2 mg./lb. of body weight of 10 per cent Anectine. The question of how much succinylcholine could be safely given to a child is not yet decided. Our clinical experience shows that 10 mg./lb. of body weight can be given safely intravenously during an operation of one to two hours' duration. In this series a child nine months old, weighing 14 lb. received 30 mg./lb. of body weight of Anectine intravenously during repair of a diaphragmatic hernia which lasted two and a half hours. The infant started spontaneous respiration ten minutes after the interruption of the Anectine drip, but needed an additional 45 minutes for full recovery of respiration. It seems that 2 mg./lb. of body weight would be quite well inside the safety limits. The injection of Anectine intramuscularly did not cause any change in pulse rate or blood pressure. But if the patient was very lightly anaesthetized, or when Anectine was given to a patient in a conscious state, there sometimes was a slowing of the heart during the intubation. In one patient there was an arrhythmia which lasted for ten minutes, until the anaes-

thesia was deepened. The arrhythmia, however, reappeared at the end of the operation one hour later. In most patients the intubation was combined with an increase in the pulse rate, and a slight increase in the blood pressure, unless the patient was heavily sedated, and induced with cyclopropane. The induction with cyclopropane, or N_2O, or Fluothane, prior to the intramuscular injection of Anectine, seems to contribute greatly to the comfort of the child. There were no differences in the time of the commencement and duration of relaxation, related to the state of consciousness at the moment of injection or intubation.

Average times before the commencement of spontaneous respiration after the intramuscular injection of Anectine, were 7½ minutes if 1 mg., 1¼ mg. or 1½ mg./lb. of body weight were given (with variations in individual cases from 3 to 18 minutes). If 2 mg./lb. of body weight were injected, the time was 10 minutes (with individual variations of 5–18 minutes), when the 2 per cent solution was used, and 11 minutes (with individual variations of 5 to 21 min.) if the 10 per cent solution was injected. This shows only 4 minutes difference in the time of appearance of spontaneous respiration in average values in 1 mg. of the 2 per cent and 2 mg. of the 10 per cent solution per pound of body weight are compared. The average times for return of adequate respiration after the injections were: 11 minutes (with individual variations of 6–15 minutes) if 1 mg./lb. was given; 12 minutes (5–15 minutes) if 1¼ mg./lb. of 2 per cent Anectine were given; 14½ minutes (10–25) if 1½ mg./lb. of 2 per cent Anectine were given; 15 minutes (10–21) if 1½ mg./lb. of 10 per cent Anectine were given; 18 minutes (14–24) if 2 mg./lb. of 2 per cent Anectine were given; 19 minutes (14–26) if 2 mg./lb. of 10 per cent Anectine were given.

It is very seldom that there is an operation where the extubation takes place in less than 20 minutes, from the beginning of anaesthesia. So even for a minor operation, if the child has to be intubated, this seems to be a time-saving procedure.

Possible Complications

It was obvious that even 2 mg./lb. of body weight of the 10 per cent Anectine solution did not cause any appreciable degree of relaxation if injected subcutaneously; therefore, a special technique for intramuscular injection was employed. If the patient was lying on the table, the injection was performed by the anaesthetist on the frontal aspect of the thigh—perpendicular to the skin, down to the bone, and then the needle was withdrawn for ½ cm. This injection may be most comfortably performed by the anaesthetist who is holding the mask on the patient's face with his left hand. In a sitting patient, the deltoid muscle or the buttock was used. For patients of one year and older a 1 c.c. syringe (tuberculine syringe) was used, in order to get exact amounts of the highly concentrated Anectine.

If too small a dosage of Anectine is given, the child will be partially paralysed and difficult to intubate. The cords may be very weak and let the tube pass easily, yet the masseter muscle may still be in spasm. If the spasm is overcome by pushing the chin downward, intubation may be easy, as the child is not capable of closing its mouth, once the laryngoscope is inserted, although he is capable

of moving his arms and legs, and may extubate himself when intubated. An additional dose of Anectine intramuscularly will relax the child within a minute, without interfering appreciably with the return of respiration. If insufficient Anectine is given, the child may resist the controlled respiration, and become anoxic.

If Anectine is given in a conscious child, the mask should not be applied immediately to the face, and assisted respiration should not be started before the relaxation starts, otherwise serious breath-holding, and laryngospasm ensue, which may last for approximately one minute. During that time the child may become very cyanotic as its increased muscular activity greatly increases the metabolism. If the anaesthetist now tries to push O_2 forcefully, he merely fills up the stomach. Therefore, the mask should be lowered gradually, and N_2O–O_2 or another non-irritating gas allowed to flow freely on to the patient's face. The mask should be applied only when assisted respiration must be started, which is obvious from the shallow diaphragmatic respiration of the patient. This occurs approximately 30 to 45 seconds after the injection of Anectine. Assisted and controlled respiration should be carried out very gently; if not, the stomach will be filled up with gas.

During the period of apnoea the depth of anaesthesia should be gradually increased, especially if ether has to be given during the operation. When the patient starts his spontaneous respirations, he may emerge from the relaxation in four to five minutes. That time may be too short to get him deep enough to tolerate the ether vapour. Struggling and breath-holding result, which may cause anoxia, or dangerous cardiac reflexes, if the concentration of the ether vapour is suddenly increased.

If during the period of apnoea the patient is deeply anaesthetized, he will not start spontaneous respiration unless the anaesthesia is lightened.

However easy the induction and intubation are made, this method is not for the beginner in anaesthesia, as with this method a good judgment of the depth of anaesthesia, as well as an estimation of respiration, is essential. Secondly, the assisted and controlled respiration in a baby needs an experienced hand. For an experienced anaesthetist it seems to be, however, a method which simplifies the induction and contributes to the safety of the grave risk patient.

Summary

In a series of 155 infants and children, relaxation for endotracheal intubation during the period of induction of anaesthesia was attained by giving succinylcholine in the form of Anectine intramuscularly.

In forty conscious patients the intramuscular Anectine was given first, followed by induction with some anaesthetic mixture by mask; but most patients were rendered unconscious before the injection, which was mainly with cyclopropane.

If the appropriate dosage of Anectine was given, all the patients were fully relaxed within two to three minutes after the intramuscular injection, and could be easily intubated.

This kind of induction was found to be especially useful in grave risk patients and cardiac surgery.

The 10 per cent solution of Anectine containing 100 mg./c.c. was used in most patients. It was found to be more effective than the 2 per cent solution, containing 20 mg./c.c.

The intramuscular doses of Anectine necessary for intubation were: 1½ mg./lb. of body weight in children three years old and younger, 2 mg./lb. of body weight in children four years and older.

The full recovery of respiration ensued within 25 minutes of the intramuscular injection.

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RÉSUMÉ

Nous rapportons une série de 155 bébés et enfants chez lesquels le relâchement pour l'intubation orotrachéale, durant le période d'induction, fut obtenu au moyen de succinylcholine (Anectine) intramusculaire. Quarante de ces patients reçurent leur Anectine intramusculaire à l'état de conscience, suivie par une induction au masque, mais dans la majorité des cas, les patients furent rendus inconscients avant l'injection, dans la plupart des cas, au cyclopropane. Avec une dose adéquate d'Anectine, tous ces patients étaient complètement relachés deux ou trois minutes après l'injection et l'intubation était très facile. Cette méthode d'induction fut particulièrement appréciée chez les mauvais risques et dans les cas de chirurgie cardiaque.

La solution d'Anectine à 10%, contenant 100 mg. au cc., fut utilisée dans la plupart des cas, et trouvé plus efficace que la solution à 2% (20 mg./1 cc.).

La dose d'Anectine intramusculaire nécessaire pour une intubation facile était de 1½ mg./1 lb. chez les enfants jusqu'à trois ans, et de 2 mg./1 lb. à compter de quatre ans.

La respiration était redevenue complètement normale au bout de 25 minutes ou moins.

FLUOTHANE TOXICITY: PATHOLOGICAL STUDIES OF MOUSE LIVER AND KIDNEY

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IT HAS been known for a number of years that halogenated hydrocarbons are capable of producing serious liver damage. Other factors such as oxygen lack or inadequate dietary intake can produce fatty degeneration. Not infrequently it is the combined effect of these factors which brings about marked pathological changes (1).

During the early phases of investigation on the halogenated hydrocarbon, Fluothane, J. Raventós (2) did some liver and kidney toxicity studies. The pathological report in his study said, in part: "The most consistent histopathological change seen in animals [rats, dogs, and monkeys] treated with Fluothane occurs in the kidney. It consists of dilatation of the proximal convoluted tubules and is associated with slight cytological change in the cells of these tubules. There are also minimal changes in the liver. These are of trivial extent and degree compared with those seen in a monkey anaesthetized on one occasion with chloroform or with changes known to occur in man after chloroform anaesthesia."

Furthermore, Raventós reported, "Microscopic examination of the livers of animals anaesthetized for long periods of time, or repeatedly, with Fluothane showed only minor change, a result that has been corroborated by biochemical tests. In no animal was fatty degeneration of the liver found, a frequent result of chloroform and divinyl ether anaesthesia."

In quest of more information on this subject, a study of the pathological status of mouse liver and kidney after exposure to anaesthetic doses of Fluothane was undertaken. Details of this investigation are the substance of this report.

METHODS OF INVESTIGATION

The experimental mice were anaesthetized in a 1 to 2 per cent Fluothane vapour. To produce adequate anaesthetic conditions a modified Kochmann (1912) apparatus was utilized. This equipment consists basically of: a syringe loaded with liquid Fluothane capable of being emptied at a constant rate; gaseous oxygen capable of being released at a relatively constant flow; a vaporizing chamber kept at a temperature slightly above the boiling point of Fluothane; a mixture chamber for O_2 and Fluothane vapour; an anaesthetizing chamber for small animals, equipped with a CO_2 absorber. This apparatus permits the administration of a controlled concentration of Fluothane-oxygen to small animals.

In all experimental animals (Tables I to IV) sections of liver and kidney were prepared as follows: (*a*) fixed in formol-alcohol, (*b*) impregnated with paraffin, and (*c*) treated with haemotoxylin and eosin stain. The livers of ten mice (Table V) were also examined by a standard fat-staining technique, that is, the tissue was (*a*) fixed in formol-saline, (*b*) quick frozen, and (*c*) stained with Sudan III.

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Standardization

Male, Fwiff albino mice of approximately 27 gm. were used throughout the experiment. They had constant pre- and post-anaesthetic care. A standard diet of Buckerfield's animal food was provided. It was noted that the eating habits of the experimental mice were not grossly altered by exposure to the anaesthetic agent.

The anaesthetic technique used was similar for all groups. The animals were exposed to anaesthetic doses of Fluothane vapour (approximately 1½ per cent) for a specified time.

Pathological examination was done by a single pathologist (Dr. Harold E. Taylor). The slides were all fixed and stained in a constant manner by the same technician. A double blind technique was utilized in presenting the slides for reading.

Experiment

Group 1. Thirty mice were anaesthetized for 45 minutes: (*a*) ten of this group were killed two days post-anaesthesia; (*b*) ten were killed five days post-anaesthesia; (*c*) ten were killed ten days post-anaesthesia (see Table I).

TABLE I

Results of Pathological Examination of Liver Tissue after 45-minute Exposure to Anaesthetic: Haemotoxylin and Eosin Stain

	Fatty degeneration	Cellular change	Normal	Total number examined
Killed 2 days post-anaesthesia	7	1	2	10
Killed 5 days post-anaesthesia	0	3	7	10
Killed 10 days post-anaesthesia	0	7	3	10

Group 2. A control group of ten unanaesthetized mice was killed after having lived ten days under standard conditions (see Table II).

TABLE II

Results of Pathological Examination of Liver Tissue in Control Group (No Exposure to Anaesthetic): Haemotoxylin and Eosin Stain

	Fatty degeneration	Cellular change	Normal	Total number examined
Killed after 10 days in the animal house under standard conditions	0	1	9	10

Group 3. Thirty mice were anaesthetized for 45 minutes on five consecutive days; total time of exposure to anaesthesia was 3 hours, 45 minutes: (*a*) ten of this group were killed two days after completion of the serial exposure; (*b*) ten were killed six days after completion of the serial exposure; (*c*) ten were killed ten days after completion of the serial exposure (see Table III).

TABLE III

RESULTS OF PATHOLOGICAL EXAMINATION OF LIVER TISSUE AFTER 45-MINUTE EXPOSURE TO ANAESTHETIC ON 5 CONSECUTIVE DAYS: HAEMOTOXYLIN AND EOSIN STAIN

	Fatty degeneration	Cellular change	Normal	Total number examined
Killed 2 days post-anaesthesia	6	2	2	10
Killed 6 days post-anaesthesia	1	2	7	10
Killed 10 days post-anaesthesia	0	2	8	10

Group 4. A repeat group of ten mice, anaesthetized for 45 minutes on five consecutive days, then killed two days post-anaesthesia, was done. This time fat stains were done on liver tissue in addition to the usual haemotoxylin and eosin stains (see Tables IV and V).

TABLE IV

RESULTS OF PATHOLOGICAL EXAMINATION OF LIVER TISSUE AFTER 45-MINUTE EXPOSURE TO ANAESTHETIC ON 5 CONSECUTIVE DAYS: HAEMOTOXYLIN AND EOSIN STAIN

	Fatty degeneration	Cellular change	Normal	Total number examined
Killed 2 days post-anaesthesia	9	1	0	10

TABLE V

RESULTS OF PATHOLOGICAL EXAMINATION OF LIVER TISSUE AFTER 45-MINUTE EXPOSURE TO ANAESTHETIC ON 5 CONSECUTIVE DAYS: SUDAN III FAT STAIN

Mouse	Results (Total involvement of lobule recorded as +4)
1	+2
2	+3
3	±
4	+1
5	+2
6	+3
7	+3
8	+3
9	+2
10	+2

Results

In the kidney studies no gross or microscopic alteration in renal structure was seen.

In the liver studies no specific alterations were found on gross examination. Microscopically three changes were noted: (i) vacuolar formation–fatty change; (ii) nuclear change–excessive numbers of binucleated cells, excessive numbers of large nucleated cells, pyknosis of nuclei excessive; (iii) zonal areas of cloudy swelling with pallor of cells.

From Tables I to IV, it will be noted that a high percentage of livers examined two days after exposure to anaesthesia showed evidence of fatty degeneration, twenty-two out of thirty. Tissue examined at longer intervals post-anaesthesia frequently showed some nuclear changes. By this time, vacuoles were no longer discernible. The fatty change produced by Fluothane in mouse liver is the usual transient type.

In group 4 (mice exposed to 45 minutes of anaesthesia on five consecutive days and then killed two days later), the fatty change observed via haemotoxylin and eosin slides correlated 100 per cent with that seen on slides prepared with special fat stains (see Tables IV and V). It will be noted that nine out of ten in this group showed fatty change. The degree of fatty change is recorded. It is graded with total involvement of a lobule indicated by +4. For details, see Table V.

Summary

A study of the pathological status of mouse liver and kidney after exposure to anaesthetic doses of Fluothane was done. The findings as recorded indicate a transient fatty change in mouse liver. This was demonstrated by vacuole formation seen on haemotoxylin and eosin slides when the experimental animal was killed two days post-anaesthesia. In the re-check series (Group 4), 100 per cent correlation between tissue stained with haemotoxylin and eosin and special frozen-section fat-stained slides was found.

No gross or microscopic alterations in kidney structure were seen.

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RÉSUMÉ

Nous avons fait une étude pour nous rendre compte de l'existence de pathologie dans le foie et les reins de souris soumises à des doses anesthésiques de Fluothane. Nous avons employé la souris comme animal de laboratoire. L'appareillage anesthésique employé était un appareil Kochmann (1912) modifié.

Nous n'avons constaté aucune modification macroscopique ou microscopique dans la structure rénale. Chez un grand nombre de souris soumises au Fluothane, nous avons constaté une franche dégénérescence graisseuse du tissu hépatique aux environs de la veine centrale. Nous avons pu faire ces constatations sur des coupes venant d'animaux tués deux jours après l'anesthésie. Lorsque les coupes de tissu venaient d'animaux tués cinq à dix jours après l'anesthésie, nous n'avons pas pu observer de formations vacuolaires. Cependant, à ce moment-là, nous avons noté sur certaines coupes des changements nucléaires, i.e., de multiples gros noyaux et de multiples cellules binucléées.

Dans les groupes de vérification (Tables IV et V), les résultats sur les coupes hemotoxylin et eosin correspondaient 100% à des préparations spéciales de trainées de graisse gelée.

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AN INVESTIGATION OF ATARAXICS IN LABOUR: MEPROBAMATE (EQUANIL®)

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IN THE SEARCH for safer and more effective methods with which to provide analgesia during labour, the staff of Vancouver Grace Hospital has conducted a number of clinical trials. These studies concerned certain of the ataractic agents, generally in combination with meperidine.

Of the numerous problems surrounding obstetrical analgesia, two factors received particular attention: (1) the principle pioneered by Grantly Dick Read, which teaches that mental and physical relaxation during labour is valuable and desirable, has been accepted; (2) there is a hard core of perinatal deaths in which hypoxia of the foetus appears to be an important if not the principal cause. By depressing the vital centres, analgesic drugs may aggravate an existing foetal hypoxia or may be wholly responsible for the reduction of blood oxygen tension in the foetus. Any improvement in obstetrical analgesia, therefore, must include decrease or even elimination of foetal depression.

This investigation concerned a trial of meprobamate (1–3)[2], an aliphatic compound unlike the phenothiazine derivatives studied previously (4). A close relative of mephenesin, meprobamate is said to act as a muscle relaxant and anticonvulsant, and to have "tranquillizing" properties (5–10).

This study was designed: (i) to assess the emotional status of the patient on admission and to observe any change after administration of the compound; (ii) to record alterations in blood pressure, pulse, and temperature; (iii) to note any side effects produced in the mother; and (iv) to evaluate the condition of the infant on delivery.

METHOD

Meprobamate was administered to seventy-four patients (fifty primiparas, twenty-four multiparas) on admission to Grace Hospital for delivery. All were admitted directly to the labour room.

The emotional status of the patient on admission was classified as: (*a*) calm, (*b*) tense, (*c*) apprehensive, and (*d*) unco-operative. The blood pressure, pulse, and temperature readings were taken on admission and recorded.

Initially, 800 mg. (two 400 mg. tablets) meprobamate were administered by mouth. Each patient was observed in one hour. Her emotional state was evaluated and the blood pressure, pulse, and temperature readings were taken and recorded. The same observations were made again two hours and five hours after the initial dose. An analgesic (such as meperidine) was administered if necessitated by increasing pain. If in the first five hours no analgesic had been given, the dose of 800 mg. meprobamate was repeated at the end of this interval.

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[2]Meprobamate is available as Equanil®, John Wyeth & Brother Limited.

The vital signs were observed and recorded frequently throughout labour. The condition of the infant was evaluated with particular regard to the presence of respiratory depression.

Results

Emotional Status

Primiparas. Of the fifty patients in this group, twenty-seven (54 per cent) were considered calm on admission and remained so throughout the period of observation. Seventeen patients were tense at the time of admission. Of these, six became calm within one hour after administration of meprobamate and an additional three within two hours. Thus nine (about 53 per cent) of the tense primiparas were relaxed within two hours after receiving meprobamate. Six of the patients who appeared calm on admission became tense in the two hours after administration of meprobamate (Table I).

Multiparas. Of this group of twenty-four patients, six were classified as tense on admission. One hour after meprobamate had been given, five had become calm and the sixth was considered calm after two hours. The other eighteen were calm throughout the first stage. Two patients in the group who were calm on admission became tense in the two hours after administration of meprobamate (Table I).

TABLE I

Analysis of Emotional Status of 74 Patients

	Primiparas		Multiparas	
	No.	%	No.	%
Total patients	50		24	
Tense or apprehensive when meprobamate given	17	34	6	25 (of 24)
Tense or apprehensive converted to calm 1 hour after meprobamate	6	35 (of 17)	5	83 (of 6)
Tense or apprehensive converted to calm 2 hours after meprobamate	3	18 (of 17)	1	17 (of 6)
Tense or apprehensive converted to calm 1 or 2 hours after meprobamate	9	53 (of 17)	6	100 (of 6)
Calm when meprobamate given*—tense or apprehensive in 1 hour	3	6 (of 50)	1	4 (of 24)
Calm when meprobamate given*—tense or apprehensive in 2 hours	3	6 (of 50)	1	4 (of 24)
Calm when meprobamate given*—tense or apprehensive in 1 or 2 hours	6	12 (of 50)	2	8 (of 24)
Calm throughout	27	54 (of 50)	16	67 (of 24)

*Most of these patients were probably apprehensive but were able to conceal their emotions. Our further observations of responses to this drug would indicate that small doses (i.e., 800 mg.) tend to reduce but not entirely to remove inhibitions. In such patients, larger doses are needed to achieve true relaxation—complete freedom from fear.

Analgesia and Hypnosis

The relaxant effects of an oral dose of meprobamate developed in about one hour and lasted about six hours. To maintain a state of tranquillity the compound was administered every five hours until need of an analgesic became apparent. Meprobamate seems to have no cumulative action, provides little sedation, and

does not potentiate the analgesic effects of narcotics. Thus larger doses of meperidine, for example, would be required to produce a satisfactory analgesia in the presence of pain than are necessary when meperidine is used in combination with promethazine (and would be accompanied by increased risk of foetal depression). Consequently, as labour progressed to the second stage in this series, and the pain increased in severity, more effective analgesia was necessary. It was decided, therefore, to substitute promethazine for meprobamate in the sedative-analgesic combination.

The lack of superiority of meprobamate as an analgesic potentiator is indicated by the fact that the average dose of meperidine required in the early first stage was little less than that used in previous trials employing meperidine with other compounds (Table II).

TABLE II

SEDATION AND ANALGESIA REQUIRED

	No. of patients	Total Meperidine (mg.)	Total Promethazine (mg.)	Total Meperidine per patient (mg.)	Total Promethazine per patient (mg.)
Meprobamate series	75	6,950	3,520	92.6	46.9
Routine sedation (4) (meperidine-promethazine)	300	29,400		98	38.5

Hypnosis is not a prominent feature of meprobamate medication. Patients who received 50 mg. promethazine by intramuscular injection later in labour showed a much more pronounced tendency to drowsiness. Meprobamate is of advantage for the patient for whom sedation is undesirable.

Duration of Labour

Meprobamate appeared to have no adverse effect on the establishment or progress of the first stage. The average total length of labour in this series was somewhat prolonged in comparison with the same observations recorded in previous studies (4) (Table III).

TABLE III

AVERAGE DURATION OF LABOUR

	Primiparas					Multiparas				
	No.	Stage 1 (hrs.)	Stage 1 (min.)	Stage 2 (hrs.)	Stage 2 (min.)	No.	Stage 1 (hrs.)	Stage 1 (min.)	Stage 2 (hrs.)	Stage 2 (min.)
Meprobamate	50	13	50	0	54	24	9	20	0	18
Routine sedation (4) (meperidine-promethazine	135	11	43	1	7	165	8	55	0	19

Delivery

Forty-nine single infants and one pair of twins were delivered to the primiparous mothers, and twenty-four single infants to the multiparous.

Among the infants of the primiparas, seven were delivered spontaneously, including one of twins; thirty-nine were delivered by low forceps, including the second twin, and two by mid-forceps; two were breech deliveries.

One primipara was eventually delivered by Caesarean section after forty-eight hours of trial labour in the first stage. A well-developed constriction ring was present. Therefore, the predelivery medication could not be held responsible for the ineffectiveness of labour in this patient.

Of the multiparas, eighteen delivered spontaneously, five were delivered by low forceps and one by mid-forceps. No abnormalities of the labour mechanism developed in this group.

Condition of Infants

There were no stillbirths and no neonatal deaths (that is, in the first seven days).

Among the fifty infants delivered vaginally of primiparous mothers, respiration occurred spontaneously (that is, within thirty seconds of delivery) in forty-five. Respiration was delayed for sixty seconds in five infants. Two of these were breech deliveries. In two infants manual rotation from the posterior position and mid-pelvic forceps delivery were performed. There was no apparent cause for the slightly delayed initiation of respiration in the remaining infant. All infants in whom breathing was delayed responded immediately to administration of oxygen by mask, and progressed normally thereafter. Intubation was not required in any case, nor was there any indication for use of nallorphine.

All infants born to multiparas breathed spontaneously within thirty seconds. In one instance meconium staining appeared at the time of delivery. The infant, however, breathed immediately and cried well. The cord was wound once around its neck.

The *blood pressure*, *pulse rate*, and *temperature* showed no significant variations in either the primiparas or the multiparas during the period of observation. In all patients the rise or fall in blood pressure was no greater than 10 mm. Hg. The pulse rate was increased or reduced by no more than ten beats per minute. Surprisingly, none of the patients who were tense on admission and who became calm after meprobamate medication showed a consistent response. These patients might have been expected to experience a slight fall in blood pressure and pulse rate in keeping with their improved state of relaxation.

Side Reactions

In general, meprobamate appeared non-toxic and free from side actions. No disturbance of gastro-intestinal function, urinary output, or lactation could be attributed to the compound.

One case of allergic dermatitis occurred. The sensitivity reaction exhibited by this patient resembled others previously reported (2, 5, 6, 8–11). Although

troublesome, the rash did not interfere with the processes of parturition. The infant was unaffected.

Other Possible Uses of Meprobamate

A patient suffering from severe toxaemia of pregnancy, who also showed a pronounced "functional overlay" of apprehension, received the conventional treatment with opiate and barbiturate drugs. When meprobamate (400 mg. three times a day) was added to the regimen, there was a definite improvement in her emotional state and her mental outlook was considerably brightened. Meprobamate apparently did not potentiate the hypotensive action of the drugs used for treatment of the toxaemia.

Summary and Conclusions

Meprobamate was used orally, early in labour, for relaxation of seventy-four patients (fifty primiparas, twenty-four multiparas). Emotional tension was relieved in a significant proportion of patients.

The findings in this study would seem to indicate that the compound should be used for the express purpose of allaying the anxiety and apprehension attendant upon the early phases of the first stage, prior to the need of analgesia. Meprobamate is neither an analgesic nor a potentiator of analgesics.

Meprobamate appears to have no deleterious effect on the mechanism of parturition or on the foetus. One patient exhibited cutaneous evidences of sensitivity. Labour proceeded normally, however, and the infant was delivered safely.

Résumé

Chez soixante-quatorze malades (cinquante primipares et vingt-quatre multipares) dans le but d'obtenir du relâchement, nous avons employé, au début du travail, du meprobamate per os. Dans une proportion importante des malades, la tension émotionnelle a été vaincue.

Les résultats de cette étude nous amènent à croire que ce médicament ne devrait être employé que dans un but précis: diminuer l'anxiété et l'appréhension des premiers moments du travail avant que l'analgésie ne soit requise. Le meprobamate n'est ni un analgésique ni un potentialisateur des analgésiques.

Le meprobamate, toutefois, ne semble pas avoir d'effets nuisibles sur le fœtus ni sur les mécanismes du travail. Une malade sensible au médicament a présenté des manifestations cutanées. Toutefois, le travail s'est poursuivi normalement et l'enfant est né sans signe de séquelles.

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A RELIABLE COLORIMETRIC METHOD FOR THE QUANTITATIVE DETERMINATION OF PROCAINE IN HUMAN WHOLE BLOOD[1]

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A REVIEW of the literature on the estimation of procaine in blood reveals that many methods have been advocated for the quantitative estimation of this local anaesthetic (1, 2, 3, 4, 5). In Table I are listed the results of some investigations that have been reported. As one studies the methods that have been published it becomes apparent that the investigators did not appreciate the rapid enzymatic destruction of procaine in human blood (6, 7, 8, 9), the adsorption of procaine on precipitated blood proteins, and the alkaline hydrolysis of procaine in solution extracted for analysis (7, 10, 11).

TABLE I

BLOOD AND PLASMA LEVELS OF PROCAINE REPORTED IN THE LITERATURE

Species	Route	Amount	Procaine (mg./100 ml. blood)	Reference
Dog	I.V.†	15 mg./kg. (309 mg.; 100 mg./min.)	1.25 (at 2 min.; 0 at 1 hr.)	12
	I.V.	1.5–2.5 mg./kg./min.	4	13
Guinea pig	I.V.	45 mg./kg. (lethal dose)	11.5	20
	I.P.†	887 mg./kg. (lethal dose)	46.3	
	I.M.†	375 mg./kg. (lethal dose)	11.0	
	S.C.†	475 mg./kg. (lethal dose)	15.7	
	S.C.	522–755 mg./kg.	8.7–11.1 (fatal in 2)	2
		96–258 mg./kg.	3.0–4.6 (toxic in 7)	
		12.1–50.6 mg./kg.	0.65–1.95 (non-toxic)	
Rabbit	S.C.	200 mg.	1.2 (50–70 min.)	14
	I.V.	20 mg./kg.	32 (0 at 30 min.)	3
	I.V.	30 mg./kg.	0.9–0.2 (5–240 min.)	15
		15 mg./kg.	0.2–0.1 (15–240 min.)	
	I.P.	60 mg./kg.	0.9 (max. at 60 min.)	
		30 mg./kg.	0.24 (max. at 60 min.)	
Cat	I.V.	0.5–2.5 mg./kg./min.	6–66 mg./l (0 at 30 min.)	18
Human	Spinal	300 mg.	0.016	1
	S.C.	2.27–13.6 mg./kg.	0.2–0.3 (2/13)	2
	I.V.	200–500 mg./25 min.	5.5–8.6	3
	I.V.	5 gm./120–405 min.	0.28–1.2 (0 at 1 hr.)	5
	I.V.	2 gm./45–125 min.	Less than 0.35 mg./l.* (0 at 1 hr.)	4

*Procaine mg./L. plasma.
†I.V. = intravenous; I.P. = intraperitoneal; I.M. = intramuscular; S.C. = subcutaneous.

INACTIVATION OF SERUM CHOLINESTERASE

It has been recognized for at least ten years that the serum esterase in human blood rapidly destroys procaine; this rapid destruction does not hold true for blood of most laboratory animals—monkeys and some of the apes being exceptions

[1]The data included herein were taken in part from a Thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy, University of Toronto, May, 1957.

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(7, 9). The optimum velocity of hydrolysis by human serum esterase alone has been estimated to be 19 mg. procaine hydrochloride per minute (8). Therefore, any method devised for the estimation of procaine should involve the arrest of enzyme activity immediately upon withdrawal of a blood sample. Methods for inactivating the enzyme have been reported by many authors (1, 3, 5, 12, 13, 14, 15), some of whom followed the Bratton-Marshall method for sulfonamides (16); others (2, 7) have added trichloroacetic acid to the blood immediately upon its removal, thus destroying the enzyme and precipitating the blood proteins. Other chemicals such as sodium arsenite (4), sodium fluoride (11, 17), and sodium fluoride–potassium oxalate solution (18) have been used to advantage to inhibit enzyme activity without precipitating proteins. It was apparent from the literature that when the sodium fluoride content of human whole blood was M/2, enzymatic procaine hydrolysis was negligible; M/20 potassium oxalate was employed in blood samples as an anticoagulant (11).

Extraction of Procaine

Each of the workers who adopted the methods listed above, regardless of whether enzyme inhibition was first accomplished or not, employed trichloroacetic acid (15–20 per cent) to precipitate the blood or plasma proteins without mentioning the possibility of procaine being hydrolysed by the acid. In order to test whether such hydrolysis occurred, trichloroacetic acid solutions (20 per cent) containing 0.2 mg. procaine hydrochloride or 0.1 mg. PABA were measured in the DK Spectrophotometer for any change in concentration and as none was apparent, it was assumed that acid hydrolysis was absent.

The filtrate obtained following the precipitation of blood proteins by trichloroacetic acid has then been used by other workers for the extraction of procaine. As a rule they have made the filtrate alkaline (pH 9 or greater) and then extracted it with chloroform (11, 15, 17) or ethylene dichloride (4) without considering any loss of procaine in this alkaline medium.

Initial experiments in this study were directed to the measurement of stability of procaine in a medium at a pH about 7. A series of procaine solutions were made up in phosphate buffer with a pH of 7.36, the concentrations of procaine base ranging from 100 mg./L. to 0.78 mg./L. Equal volumes of procaine-base solution and chloroform were shaken together vigorously after which spectrophotometric analyses in the DK Spectrophotometer were carried out on the chloroform layers. If the original procaine dilution was greater than 15 mg./L., the chloroform layer was then diluted with chloroform so that the concentration of procaine was 10 mg./L. The heights of the curves were proportional to the procaine concentrations and were so similar to curves obtained with aqueous solutions of procaine at the same pH values that loss of procaine could be considered to be negligible.

The recovery of PABA was determined in a like manner. After a phosphate buffer solution (pH 7.36) containing 3.3 μg. PABA was extracted with chloroform on a roller extraction apparatus for one hour, only 0.8 per cent was

recovered, a quantity much less than that reported (10) for a chloroform-isopropanol solvent (10 per cent PABA at pH 7.0 and 5 per cent at pH 7.5). Thus chloroform alone appears to be a favourable extracting solvent for procaine at a pH of 7.36, removing only a negligible amount of PABA.

In the present procedure, chloroform removes unknown substances from blood together with procaine; these pass into a N/20 hydrochloric acid extract of the chloroform and may be removed by shaking the aqueous extract with ether. A control extraction made on an N/20 hydrochloric acid solution containing 3.3 μg. procaine showed that no measurable quantity of procaine was removed by the ether.

Methods Demonstrating the Presence of Procaine in Solution

The quantity of procaine in solution may be estimated in two ways, either by measuring its disappearance when broken down by an enzyme or by alkali per unit time, or by estimating the amount actually present in the solution following the formation of an azo dye from it. The methods recommended for this purpose have been tried and are reported below.

Esterase Method

To determine the efficacy of the esterase method, an esterase solution is made up by adding 0.25 ml. Cholase (trade name for plasma cholinesterase) to 75 ml. distilled water. This solution is equal in cholinesterase activity to that of undiluted human plasma. Following the addition of such a solution to a procaine solution, the rate of breakdown of procaine could be measured in the DK Spectrophotometer (290 mμ) and the loss of procaine estimated for the first four minutes at thirty-second intervals and at the end of two, four, six, and twenty-four hours. It was found that in ten solutions thus analysed the reading at the 24-hour period indicated a higher concentration of procaine than was present at the end of the two-hour period; it was then learned by spectrophotometric examination (DK) that this substance was not procaine. It was therefore assumed that in the 24-hour period some other material had accumulated and to determine the loss in procaine the final readings should be taken at the end of two hours.

Diazotization

This method appears to be the most popular among investigators. It is valuable for determining diazotizable primary aryl amines with a free amino group or a blocked amino group which can be detached by hydrolysis. The reaction occurring is indicated in Figure 1. Procaine is diazotized with sodium nitrite in acid solution, the excess nitrite being removed with ammonium sulfamate to prevent formation of nitroso compounds which would inhibit coupling. Following this, coupling components (19) can be added, that chosen in this experiment being N-(1-naphthyl)-ethylenediamine dihydrochloride which forms an azo dye (purple) upon coupling; this coupling proceeds most rapidly in the pH range of 1 or 2 in the presence of hydrochloric acid. The peak of absorption for N-(1-naphthyl)-ethylenediamine hydrochloride is reported to be 545–550 mμ (11, 16).

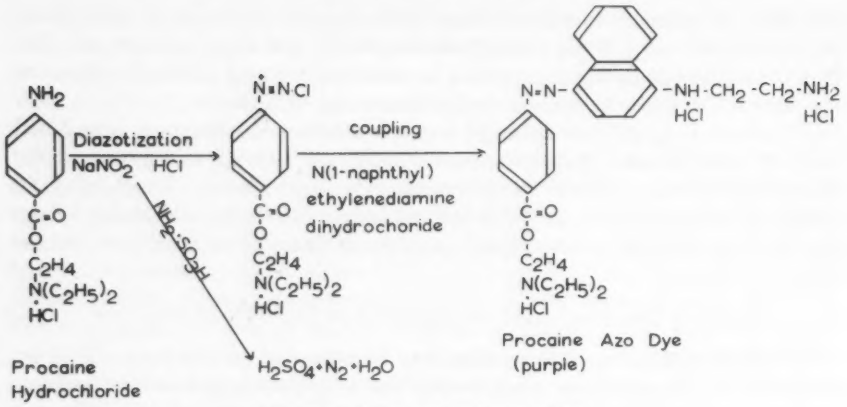

FIGURE 1. Diazo reaction for procaine.

A series of test solutions were made up containing 10 μg./ml. to 1.156 μg./ml. of procaine hydrochloride. In the analysis, one drop of 1 N hydrochloric acid, the sodium nitrite, ammonium sulfamate, and N-(1-naphthyl)-ethylenediamine dihydrochloride were added in order, to 3 ml. of procaine hydrochloride solutions; the amounts and concentrations of the coupling reagents are recorded in the modified procedure described later. The blank consisted of 3 ml. water plus one drop of 1 N hydrochloric acid and the other reagents. The optical densities were measured in the DU Spectrophotometer and the readings thus obtained were plotted against the concentration of procaine hydrochloride (Fig. 2). A straight line was obtained passing through the origin, indicating a direct relation between optical density and concentration of procaine solution. This method was the simplest for measuring concentrations of procaine.

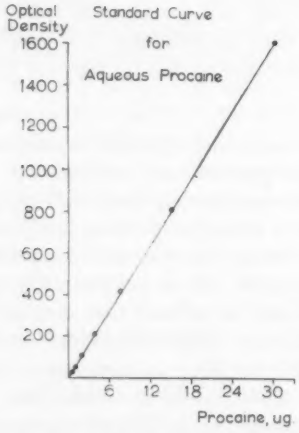

FIGURE 2. The direct relationship between procaine concentration and optical density.

Since samples of blood containing procaine were withdrawn from patients receiving pentobarbital and meperidine, trials were made to ascertain whether these drugs singly or combined would interfere with the method outlined later. Since no interference was found and since sulfonamides were not administered to these patients, it was assumed that this method was satisfactory for the analysis of procaine in blood of persons to whom the drug had been administered.

Quantitative Determination of Procaine in Human Blood

Reagents

1. A solution of sodium fluoride-potassium oxalate containing 8.4 gm. sodium fluoride and 3.68 gm. potassium oxalate dissolved in 250 ml. distilled water
2. Chloroform and ether solvents
3. Hydrochloric acid N/20
4. A 0.1 per cent solution of sodium nitrite
5. A 0.5 per cent solution of ammonium sulfamate
6. A 0.1 per cent solution of N-(1-naphthyl)-ethylenediamine hydrochloride which should be kept in the dark

Procedure

To 5 ml. of sodium fluoride–potassium oxalate solution, 3 ml. of blood are added to give a final concentration of M/2 sodium fluoride and M/20 potassium oxalate (pH 7.9). Chloroform 50 ml. is then added to this mixture and the solution is rolled in a suitable bottle on a roller extraction apparatus for one hour, at the end of which time 40 ml. of chloroform are removed. A further extraction employing 40 ml. of chloroform is carried out, rolling for fifteen minutes, after which time 40 ml. of chloroform are again removed. The combined chloroform extracts of 80 ml. are added to 4 ml. of N/20 hydrochloric acid in a separatory funnel. After adequate agitation of the contents, the lower chloroform layer is drawn off and discarded. Solvent ether 3 ml. is then shaken with the acid solution in the separatory funnel to remove any interfering materials which might be present. The lower acid layer is drawn off and freed from any remaining chloroform or ether by evaporation before a fan until the odour of the solvents is no longer present. A blank which is to be used for the zero setting contains 3 ml. of N/20 hydrochloric acid. The following reagents are then added in order to 3 ml. portions of the acid or blank: 0.15 ml. of sodium nitrite solution and allow to stand for five minutes; 0.15 ml. of ammonium sulfamate solution and allow to stand for three minutes; 0.15 ml. of N-(1-naphthyl)-ethylenediamine dihydrochloride solution and allow to stand for twenty minutes for full colour development. The optical densities are measured in the DU Spectrophotometer at 550 mμ wave length and 0.02 mm. slit width, using a tungsten lamp as a source of light.

Preparation of a Standard Curve for Procaine Extracted from Whole Blood

A graph was prepared with a standard line from which readings could be transposed to quantities of procaine (Fig. 3). For this purpose a procaine solu-

tion containing 20 mg./L. was prepared so that accurate concentrations could be made readily by suitable dilutions. Each of three blood samples 1.5, 3.0, and 6.0 ml. was diluted with procaine so that in each blood sample there were 20, 10, and 5 μg. procaine respectively; for background determinations blood samples were diluted with 1 ml. of water. Percentage of recovery by this method was estimated as follows. The curve for the recovery of procaine from blood was plotted as is shown in Figure 3 (*b*, *c*). On the same day a curve was made using the same chemical procedure as outlined on 20, 10, and 5 μg. procaine in N/20 hydrochloric acid. The curve for these results is also shown in Figure 3 (*a*).

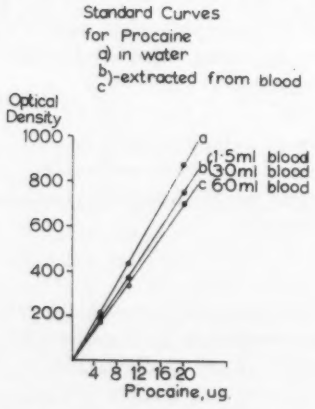

FIGURE 3. The recovery of procaine from water and human whole blood.

Using the two curves (*a* and *b* or *c*) the recovery was calculated as follows. A point on the curve obtained with the blood samples (1.5 and 3.0 ml.) corresponding to 10 μg. procaine was extrapolated towards the curve of procaine in hydrochloric acid solution parallel to the abscissa. From the point of intersection a line was drawn down perpendicular to the abscissa where the amount of procaine was read to be 8.6 μg. However, since only 40 of the 50 ml. of chloroform were drawn off for the first extraction, the amount of procaine of the original 10 μg. removed at this stage would be $40/50 \times 10 = 8$ μg., leaving 2 μg. for the second extraction with chloroform; the amount of procaine removed from the second extraction would be $40/50 \times 2 = 1.6$ μg. Therefore, the total amount of procaine expected from the two extractions with chloroform without any loss should be $8 + 1.6 = 9.6$ μg. Thus, the 8.6 μg. above obtained from the graph corresponds to 90 per cent of the expected value (9.6 μg.), indicating that 10 per cent loss occurs during the extraction procedure.

While it is evident that the percentage recovery from 6 ml. blood is comparable to that from 1.5 ml. blood, it was found that the second extraction with chloroform was more difficult since emulsification occurred. It was, therefore, decided that blood samples from patients would be in the order of 3 ml. and for greater accuracy the blood would be measured by weight rather than by volume.

Method of Withdrawing Blood Samples from the Arm Vein of a Patient

It was recognized that certain errors were bound to occur in the estimation of the concentration of procaine in samples of blood drawn from patients into whom procaine had been injected, because the esterase in the blood would be destroying the procaine during the interval of drawing the sample and transferring it to the sodium fluoride–potassium oxalate solution where the enzyme would be destroyed.

The procedure adopted was one in which two syringes connected with suitable stop-cocks were joined to a catheter remaining in the vein during the sampling time (Fig. 4). One syringe was filled with saline in order to flush out the catheter, the other was employed to withdraw a blood sample rapidly and to transfer it to the sodium fluoride–potassium oxalate solution in the minimum amount of

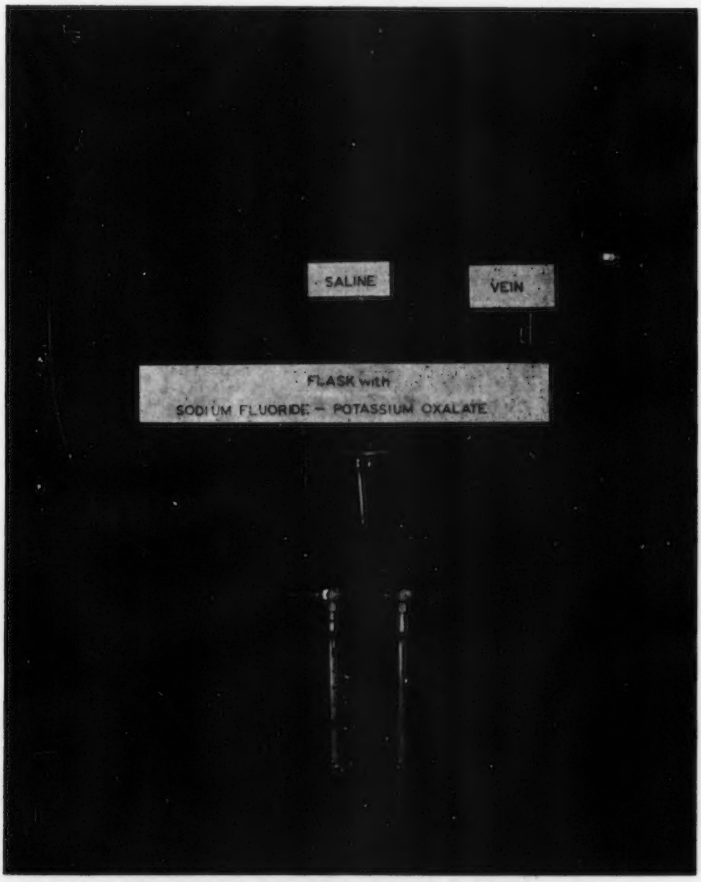

Figure 4. Apparatus used for withdrawing blood samples from the arm vein of a patient.

time. Time was recorded on the stop-watch from the moment infiltration of procaine (2 per cent solution) was begun; about two minutes were required to complete the subcutaneous infiltration and during this interval the greater part of procaine hydrochloride was injected, varying from 1.7 to 2.5 gm. Subsequently small amounts were infiltrated and on occasion the total amount injected rose to 3.7 gm. The blood samples were timed from the beginning of infiltration to the time when one-half of the blood in the syringe had been transferred to the sodium fluoride–potassium oxalate; the time interval between samples was approximately five minutes. A control sample of blood for analysis was drawn from each patient prior to the injection of procaine.

These investigations were made on male patients undergoing hernia repair, ranging in age from 25 to 50 years, weighing from 148 to 190 lb., and with heights of 5 ft. 6 in., to 6 ft.

Results

The recovery of procaine in these studies is tabulated in Table II and some of the results are presented graphically in Figure 5. These curves were obtained by

TABLE II

Concentration of Procaine in Whole Blood of Surgical Patients after Infiltration Anaesthesia

Age (yrs.)	Weight (lb.)	Height (ft.)	Height (in.)	Total amount injected (gm.)	Peak concentration in blood (μg./gm. blood)
35	149	5	10.5	3.7	3.0
25	178	6	0	2.8	2.1
35	173	5	6	3.0	1.9
41	185	5	10	3.2	2.2
25	190	5	9	2.9	5.1
36	169	5	10	3.0	1.5
48	170	5	8	3.2	3.2
48	148	5	6	2.06	1.5
39	122	5	7	2.9	2.4
50	160	5	7.5	2.6	0.7
26	175	5	11	2.4	0.7

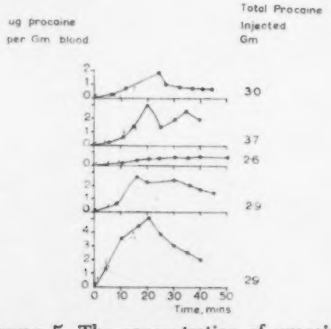

Figure 5. The concentration of procaine in the blood of patients during hernia repair under local anaesthesia.

plotting the concentration of procaine determined in the blood at various time intervals after the subcutaneous infiltration of procaine. It will be noted that a peak concentration was reached approximately 20 minutes (15–25 minutes) after the injection of procaine; the peak concentration varied from 0.7 to 5.0 μg. procaine per gram of blood.

Discussion

The method described was employed following a critical examination of other methods reported in the literature, which had been used chiefly for the estimation of procaine injected intravenously. It is believed that by the use of the method described we have estimated with a reasonable degree of accuracy the concentrations of procaine in the blood of patients to whom large amounts of procaine have been given by infiltration. The variation seen in the peak concentration (0.7 μg. to 5.0 μg. per gram of blood) may be due to a variation in the serum cholinesterase levels in the blood of the different individuals or in the amounts of procaine injected. Further investigations could be designed to determine esterase levels and to follow the procaine concentration in the blood after a single dose of procaine.

Summary

A method which has been developed for the satisfactory estimation of procaine in whole blood avoids the loss of procaine which was apparent in methods where blood proteins were precipitated by use of trichloroacetic acid. Approximately 85 per cent of the added procaine was constantly recovered by this method from test samples of blood and the procedure was considered to be satisfactory for determining concentrations of procaine in patients' blood. The peak concentration of procaine in blood twenty minutes after the infiltration of procaine (2.06–3.7 gm.) varied from 0.7 μg. to 5.0 μg. per gram of blood in the patients studied.

Résumé

Nous avons mis au point une méthode précise pour mesurer, dans le sang total, la quantité de procaïne qui s'y trouve à la suite de filtrations locales de procaïne au cours de la chirurgie. Nous exposons les progrès de cette méthode et citons les publications de d'autres méthodes. Nous avons recouvré 85% de la procaïne ajoutée à des échantillons de sang humain total, ce qui indique bien que cette méthode est satisfaisante.

La concentration maximale de procaïne, variant entre 0.7 mg. et 5.0 mg. par gramme de sang humain total, a été atteinte environ vingt minutes après l'infiltration souscutanée de chlorhydrate de procaïne (2.06 à 3.7 gm.) chez des malades subissant une cure de hernie.

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OBITUARY

DR. ROMÉO ROCHETTE

On December 12, 1958, Dr. Roméo Rochette died in the Hôtel-Dieu Hospital, Montreal, where he had served as Anaesthetist-in-Chief. He was 63 years of age.

Dr. Rochette was born at Napierville, Quebec, where his father, Dr. David Rochette, practised medicine and where his grandfather had also practised medicine. Not many years after the birth of Roméo, his father moved to Terrebonne, Quebec.

After brilliant studies at the Collège de Montréal, Roméo Rochette started the study of medicine at the University of Montreal, where in 1922 he obtained the degree of Doctor of Medicine. Intern at the Hôtel-Dieu from 1921, he became chief intern in 1924, a post which he occupied until 1926 when a place as an assistant in anaesthesia was offered him. At that time specialization in anaesthesia was not well enough recognized to offer full occupation; so Rochette took up general practice for a short time.

Dr. Charles Larocque, who had started anaesthesia as a specialty in 1907 at the Hôtel Dieu Hospital and who had later taken on Dr. Adrien Larose as an assistant, soon found that he needed more help. He engaged Dr. Rochette because of his great probity and high professional conscience.

Larocque died in 1932 and Larose in 1934. From this date Rochette, then aged thirty-nine, became Chief-of-Service in Anaesthesia at the Hôtel-Dieu. Amenable, polite, and refined, Rochette always surrounded himself with a remarkable group in which one could feel the respect and the devotion commanded by the chief.

Although faithful to his duties in a large hospital as chief anaesthetist, Rochette followed diligently the progress in knowledge leading to advancement in anaesthesiology, that is, he held himself *au courant* with modern methods; and, while

he was modestly retiring and not much inclined to take part in discussions at meetings, he was, nevertheless, a good teacher in his quiet, inspiring way. Besides, he wrote well and contributed considerably to the *Journal de l'Hôtel-Dieu*. His writings mark some dates in the history of anaesthesia.

Dr. Roméo Rochette was held in the highest regard by his colleagues and he was loved by his patients as his natural tenderness inspired confidence. His work which he accomplished so marvellously was indeed *l'œuvre d'un artiste*—it expressed an extraordinary spirit of observation with an experience which nothing can supply.

The death of Roméo Rochette leaves a great void in the service of anaesthesia especially among the French Canadians and also among many of the English-speaking anaesthetists for he often attended our meetings and we often held joint meetings. Roméo was distinguished and highly cultured. He was a devoted and sincere friend, esteemed and admired colleague, and an exemplary husband. He leaves a lively remembrance in the hearts of many people, in all walks of life, who have been touched by his gentleness, his competence, and his goodness. We all join in offering again to his devoted wife, Geraldine, and to the Rochette family, our sincere condolences.

LE DOCTEUR ROMÉO ROCHETTE

A L'ÂGE de soixante-trois ans, le 12 décembre 1958 s'est éteint après une maladie de trois mois le docteur Roméo Rochette. Il est mort à l'Hôtel-Dieu, où il était anesthésiste en chef.

Fils et petit-fils de médecin, le docteur Rochette naquit à Napierville, où son père le docteur David Rochette exerça la médecine avant d'aller, quelques années après la naissance de Roméo, se fixer à Terrebonne.

Roméo Rochette, après de brillantes études au collège de Montréal, s'inscrivit à la Faculté de Médecine de l'Université de Montréal, où il obtient en 1922 son doctorat en médecine.

Interne à l'Hôtel-Dieu dès 1921, il en devint le chef interne en 1924, poste qu'il occupa jusqu'en 1926, alors qu'une place d'assistant bénévole en anesthésie lui fut offerte. C'était l'époque où la spécialisation n'était pas tellement reconnue et n'arrivait pas à faire vivre son homme; si bien qu'en plus d'assurer le service d'anesthésie à l'Hôtel-Dieu, Roméo Rochette dût ouvrir un cabinet de consultation et s'astreindre à la pratique générale. Expérience qu'il connaissait bien pour l'avoir vécue chez son père, mais à laquelle il ne se sentait nullement appelé. Moins d'un an plus tard, il avait cessé de se considérer au rang des médecins praticiens. Il n'avait pu se faire aux exigences de la fonction et déjà pris par son travail à l'hôpital, il se sentait incapable de faire bien et l'un et l'autre.

Remarquable pour sa grande probité et sa haute conscience professionnelle, il avait fortement impressionné le chef du service d'anesthésie, le docteur Charles Larocque qui, débordé d'ouvrage, cherchait un assistant capable d'être toujours sur la brèche, car celui qui en fait lui servait d'aide, le docteur Adrien Larose, n'avait pas de santé et s'absentait fréquemment du service, alors que celui-ci augmentait de jour en jour.

Larocque offrit alors à Rochette une compensation pécuniaire qui puisse l'arracher à la pratique générale et le river à la collaboration hospitalière. Rochette accepta ce *modus vivendi*, qui paraît modeste à l'optique de 1958, mais qui s'avérait intéressant pour l'époque. De ce temps jusqu'à la mort de Larocque en 1932, Rochette servit l'anesthésie et son patron; il fut loyal à l'une et à l'autre. Heureux de consacrer à l'hôpital la totalité de ses efforts, il se sentait intégré à celui-ci et le progrès de l'Hôtel-Dieu était le mobile qui lui faisait rechercher les moyens d'améliorer la spécialité qu'il avait choisie.

Larocque mourut en 1932, Larose en 1934, si bien qu'à cette date, Roméo Rochette, jeune, alors âgé de trente-neuf ans, devint chef du service d'anesthésie de l'Hôtel-Dieu. Ce service, dont on peut dire qu'il a été le fondateur, a pris depuis un rayonnement extraordinaire. Homme amène, poli, délicat, Rochette sut s'entourer d'une équipe remarquable au sein de laquelle on sentait le respect et le dévouement envers le chef.

Bien qu'empêché, par les nécessités du service local, de poursuivre à l'extérieur des études post-scolaires, le docteur Roméo Rochette sut toujours se tenir au courant des méthodes modernes. La grande timidité dont il n'a jamais su se guérir l'empêcha de prendre souvent la parole aux congrès d'anesthésistes et de participer comme il l'aurait voulu à l'enseignement. Il n'avait pas le don de la parole, mais il savait écrire et le *Journal de l'Hôtel-Dieu* a publié des écrits qui lui font honneur et qui marquent des dates dans l'histoire de l'anesthésie.

Le docteur Roméo Rochette ne s'est jamais senti l'âme d'un lutteur; il croyait à la victoire de ses idées par le respect qu'il accordait à celles des autres et par la recherche de solutions qui guérissaient sans blesser. Ses collègues peuvent lui rendre cette justice d'avoir dirigé le service beaucoup plus en misant sur la concorde que sur la force. Il était aimé de ses patients, car sa douceur naturelle inspirait la sympathie et attirait la confiance. Le docteur Roméo Rochette au dire de ceux qui sont qualifiés pour juger, fut un anesthésiste hors-pair; tout bonnement, Roméo disait qu'il était incapable d'expliquer le mécanisme de son anesthésie; il se sentait incompétent à l'expliquer en termes scientifiques et déplorait de ne pouvoir transmettre aux jeunes sa technique personnelle.

Il ne savait pas que le travail qu'il accomplissait si merveilleusement était l'œuvre d'un artiste. L'anesthésie de Rochette était le fait de l'art doublé d'un esprit d'observation extraordinaire et d'une expérience à laquelle rien ne peut suppléer.

La mort de Roméo Rochette laisse un vide considérable dans le service d'anesthésie; on pourra lui succéder, il sera difficile de le remplacer. Homme distingué et hautement civilisé, ami dévoué et sincère, collègue estimé et admiré, époux exemplaire, Roméo Rochette laisse un souvenir au sein de l'Hôtel-Dieu. Administration, religieuses, médecins, infirmières, patients, tous ont été touchés de sa gentillesse, de sa compétence et de sa bonté et ils redisent à son épouse et à la famille Rochette l'expression de leurs plus sincères condoléances.

EDOUARD DESJARDINS, M.D.

BOOK REVIEWS

HOSPITAL PLANNING FOR THE ANESTHESIOLOGIST. By William H. L. Dornette, M.D. Springfield, Ill.: Charles C. Thomas [Toronto: Ryerson Press]. 1958. $5.75.

This book of 119 pages has been very thoughtfully and carefully written and, obviously, has been produced following a great deal of concentration and experience in planning not only for the anaesthesiologist but for all departments of a hospital.

No two hospitals are alike in their requirements, location, or over-all physical setup, so that adaptations of theoretical requirements have to be made to suit local circumstances. For the first time an anaesthesiologist has written a volume which can be used and should be read by anyone planning either a completely new hospital or alterations to an older setup. In a total of twenty-seven chapters, the author not only deals with operating rooms and facilities for recovery and intensive care, but goes into matters of general planning—communication systems, ventilation and air-conditioning, transport of patients, clinical laboratories and bloodbanks, emergency suites, planning for local disasters, and many other pertinent subjects.

This is a book well worth reading by anyone, whether anaesthesiologist or not, who is concerned with hospital planning either for new buildings or for remodelling old ones.

S.M.C.

PHYSIOLOGY OF SPINAL ANAESTHESIA. By Nicholas M. Green, M.D. Baltimore: Williams and Wilkins Company [Toronto: Burns & MacEachern]. 1958. Pp. 195. $6.00

This is a very comprehensive and readable review of the subject of spinal anaesthesia. It embodies an extensive review of the literature pertaining to the effects on the central nervous, cardiovascular, and respiratory systems; changes in hepatic, renal, and endocrine functions; with a special chapter on obstetrical physiology. The text, even with interruptions for hundreds of references, is easily followed and arguments for and against are clearly defined. Although spinal anaesthesia has lost its popularity in some areas, the information presented is also largely applicable in the use of ganglionic blocking agents and peridural anaesthesia. The book should be read and studied by all students, practitioners, and specialists in anaesthesia.

S.L.V.

CYCLOPROPANE ANAESTHESIA. By B. H. Robbins. Second edition. Baltimore: Williams & Wilkins Co. [Toronto: Burns & MacEachern]. 1958. $9.00.

This book is the second edition of a classic in the anaesthesia literature. Initially, one is surprised to find that current interests would justify this new edition. However, the preface quotes statistics indicating that more cyclopropane is being used than ever before!

This volume can be recommended, unreservedly, as a well-produced, authoritative reference book on all matters relating to cyclopropane. The physiological effects of this agent on each system are discussed separately, and in addition there are chapters on the clinical problems involved. Of the latter, a chapter on muscle relaxants appeared a little irrelevant at times.

In searching for ten random items of information, the reviewer found no omissions and, on the contrary, found the bibliography most comprehensive and helpful.

H.B.F.

VARIED OPERATIONS. By HERBERT A. BRUCE. Toronto: Longmans, Green & Co. 1958. $6.00.

Varied Operations is the autobiography of a distinguished Canadian who has made an enviable place for himself not only in his chosen profession but in several other aspects of the society of his time. Dr. Bruce was for many years Associate Professor of Clinical Surgery at the University of Toronto and was for a time a member of the Board of Governors of that institution. As a mark of his achievements the degree of LL.D. was conferred on him by no less than three Canadian universities. His activities were by no means confined to the practice of surgery. Perhaps no other Canadian physician has been so prominent in so many and so varied fields; certainly few have made as great an impact on society at large in their generation.

The attraction of the book for many will be the picture it presents of Ontario ninety years ago. The medical reader of the younger generation will be keenly interested in the author's accounts of his medical school days, his early life as a surgeon at Toronto, and of the several teaching hospitals which have since grown to large proportions. There is much of interest for all readers, particularly those more politically minded, in the author's notations of the various causes which he espoused over the years—principles on which he took an unwavering stand. His service as Lieutenant-Governor of the Province of Ontario, his election to the House of Commons, and his place in Toronto society brought him into contact with numerous interesting personalities, many of them world-renowned. Scattered throughout the book are anecdotes, often amusing, relating to these individuals. All readers will find much of interest in these aspects of Dr. Bruce's autobiography.

Dr. Bruce was at all times fearless in expressing his opinions whether these were related to medical, political, or social matters. In consequence on occasions he found himself the target for adverse criticism from various quarters. He was not one to shrink from such attacks, but vigorously defended his positions. It is to his credit that subsequent events often justified the stands he so firmly took. However, medical readers of an age to recall certain bitter controversies in connection with medical affairs, here dealt with in some detail, disputes in which physicians of some prominence were involved, may feel that these wounds long since healed had been better left unprobed. In particular with reference to the reorganization of the Medical Faculty in 1921, most will no doubt be of the

opinion that while certain injustices may have been apparent at the time, the appointment of full-time professors in the three major departments of the Faculty has proven to be of outstanding value to the Medical School. These chairs have been occupied by a succession of professors, renowned outside as well as inside Canada. Dr. Bruce at that time was apparently unsympathetic towards this innovation.

Regardless of his medical, political, or social views, the reader will find much of interest in Dr. Bruce's autobiography. It is most readable and never dull.

H.J.S.

NEWS LETTER

British Columbia Division

Membership of the B.C. Division, Canadian Anaesthetists' Society, now totals 114, 16 of these being Members Elect. The B.C. Division has seven business and scientific meetings scheduled for the 1958–9 session.

September 19, 1958—Dr. Harold Rice, Research Director, St. Paul's Hospital, Vancouver, B.C., "This Will Take Your Breath Away" (A Review of Pulmonary Function Tests)

October 17, 1958—Dr. J. G. Foulks, Professor of Pharmacology, University of British Columbia, "The Newer Concept of Shock Mechanism"

January 23, 1959—Dr. A. W. Conn, Hospital for Sick Children, Toronto, "Anaesthesia for Cardiovascular Surgery"

February 20, 1959—Dr. F. P. Haugen, Division of Anesthesia, University of Oregon Medical School, Portland, Oregon, "Recent Trends in Anaesthesia"

March 24, 1959—Dr. P. R. Bromage, Royal Victoria Hospital, Montreal, "On Kicking against the Pricks"

April 18, 1959—Victoria Meeting

May 30, 1959—Annual Dinner Meeting

Dr. David Allan is completing his residency training in anaesthesia at the Hospital for Sick Children in Toronto.

Dr. Gordon J. Fyffe and Dr. James A. Gibson, who recently received their certification, have established a private practice of anaesthesia in the new Surrey General Hospital.

Dr. A. K. Gibbons is associated in practice with Dr. J. J. Carroll and Associates at Grace and Burnaby Hospitals.

Dr. L. C. Jenkins, who recently returned from a McLaughlin Travelling Fellowship in Anaesthesia has joined Associated Anaesthetic Services and the Department of Anaesthesia, Vancouver General Hospital.

Dr. Irene Millar is completing her anaesthesia training at the Hospital for Sick Children, Toronto.

Dr. M. L. Miller, who recently received her certification, has left for a year of travel in Great Britain and Ireland.

Dr. R. S. Moir, who recently completed his fellowship training has joined Dr. J. J. Carroll and Associates at Grace and Burnaby Hospitals.

Dr. D. A. Walker is completing his anaesthesia training at the Sick Children's Hospital in Los Angeles.

Dr. H. A. Kester has been elected Vice-Chairman of the Western Biennial Conference.

Dr. J. B. Fulton and Dr. H. B. Graves have been elected Governors of the Western Biennial Conference.

Saskatchewan Division

The Annual Meeting of the Section of Anaesthesia of the College of Physicians and Surgeons of Saskatchewan was held on October 15 in Regina.

Dr. L. C. Skinner of Maryfield is in training with the Associate Anaesthetists in Regina.

Dr. J. Pearson arrived from England in October to join the Department of Anaesthesia, University Hospital, Saskatoon, as Assistant Resident.

Dr. Allen B. Dobkin was invited to take part in the programme of the Congress of Brazilian Anesthesiologists which met at Recife, Pernambuco, Brazil, from November 9 to 15. He discussed the role of the anaesthetist in the management of severe respiratory depression.

Dr. F. C. Haley was appointed Instructor in Anaesthesia in the Department of Anaesthesia at the University Hospital, Saskatoon, upon completion of his residency.

New Brunswick Division

We welcome two new members to the division, Dr. Jean Caron is practising in Bathurst, and Dr. Egbert Daigle has joined the Moncton Anaesthetic Service, and will be working mainly at the Hôtel Dieu in Moncton.

Work is progressing on schedule for the Maritime Meeting to be held at the Brunswick Hotel in Moncton, April 17 and 18. Members outside the Maritimes will be welcome, and can obtain more information from Dr. J. A. Dobson, 521 Blythwood Avenue, Moncton, N.B.

CANADIAN ANAESTHESISTS' SOCIETY ANNUAL MEETING
MAY 4 TO 7, 1959

TENTATIVE PROGRAMME

Monday, May 4

9:00 A.M. Registration and visiting exhibits
9:30 A.M. Council Meeting

2:00 P.M. "The Problems of Tonsillectomy Haemorrhage"—Dr. H. T. Davenport
2:30 P.M. "Indications for the Use of Fluids and Blood before and during Surgery"—Dr. T. H. Seldon
3:00 P.M. Break for visiting exhibits
3:30 P.M. "The Analeptic Effect of L.S.D.25: A Clinical and Experimental Evaluation"—Dr. Allen B. Dobkin
4:00 P.M. "The Numerous Possibilities in the Field of Reanimation"—Dr. Lucien Rinfret

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Tuesday, May 5

9:30 A.M. Round Table: "What is the Place of the Mechanical Ventilator in Anaesthesia?"
10:30 A.M. Break for visiting exhibits
11:00 A.M. Annual General Meeting.

2:00 P.M. "A Respiratory Therapy Unit"—Dr. H. B. Fairley
2:30 P.M. "Infant Survival in 700 Caesarean Sections"—Dr. G. V. Parsons
3:00 P.M. Break
3:30 P.M. "Axillary Block"—Dr. Fernando Hudon
4:00 P.M. "Contrôle de la pureté des substances anesthésiques"—Dr. J. G. Patoine

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Wednesday, May 6

9:30 A.M. "Experience with Fluothane-Ether in Lung Surgery"—Dr. J.-P. Dechêne
10:00 A.M. "Fluothane in Obstetrical Anaesthesia"—Dr. J. G. Robson
10:30 A.M. Break
11:00 A.M. "Mepazine, Meperedine, and Dihydrocodeine in Labour"—Dr. Ian Purkis
11:30 A.M. "A Comparative Clinical Study of Three Analgesic Drugs"—Dr. C. W. P. Lunderville

2:00 P.M. "Plasma Adrenalin and Noradrenalin Levels during Clinical Anaesthesia"—Dr. R. A. Millar

2:30 P.M. to 4:00 P.M. Historical, Pharmacological, and Clinical Review of Cyclopropane—Dr. H. R. Griffith, Dr. George Lucas, Dr. E. A. Gain

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Thursday, May 7

9:30 A.M. *Work in Progress*

9:30 A.M. "Delayed Death"—Dr. Paul Quan

9:45 A.M. "Further Work on the Use of Intramuscular Succinylcholine for the Induction of Anaesthesia in Children"—Dr. J. Beldavs

10:00 A.M. "Dimenhydrinate Potentiation in Anaesthesia"—Dr. G. Fortin

10:15 A.M. Break to visit exhibits

11:00 A.M. "Safe and Economical Method of Administering Fluothane in Closed Circuit Anaesthesia"—Dr. A. Romagnoli

11:15 A.M. "Cardiovascular Effects of Azeotropic Fluothane-Ether"—Dr. Gordon Wyant

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2:30 P.M. Meeting of Council

EXAMINATION RESULTS

THE FOLLOWING CANDIDATES were successful in the 1958 Examinations of the Royal College of Physicians and Surgeons of Canada in the Specialty of Anaesthesia.

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THE CANADIAN ANAESTHETISTS' SOCIETY JOURNAL

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